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Faculty: international
Department Internal medicine 1 with the cardiovascular pathology course

CONFIRMED by
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METHODOLOGICAL DEVELOPMENT TO THE LECTURES ON THE EDUCATIONAL DISCIPLINE

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Lecture № 1

Topic: Essential hypertension

Actuality of theme: Hypertension is a major public health problem and important area of research due to its high prevalence and being major risk factor for cardiovascular diseases and other complications. Hypertension is a major public health problem due to its high prevalence all around the globe. Around 7.5 million deaths or 12.8% of the total of all annual deaths worldwide occur due to high blood pressure. It is predicted to be increased to 1.56 billion adults with hypertension in 2025.

Raised blood pressure is a major risk factor for chronic heart disease, stroke, and coronary heart disease. Elevated BP is positively correlated to the risk of stroke and coronary heart disease. Other than coronary heart disease and stroke, its complications include heart failure, peripheral vascular disease, renal impairment, retinal hemorrhage, and visual impairment

Goal: explain the essence of the hypertension, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention.

Key words: essential hypertension, renin-angiotensin-aldosterone system, systolic blood pressure, diastolic blood pressure, antihypertensive drugs

Lecture plan and organizational structure

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: Relevance of the topic Definition Classification Etiology and main links of pathogenesis Symptoms and signs Diagnostic criteria Main syndromes and differential diagnosis Criteria for the severity of disease	 II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

	Treatment Prevention	II II		
III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Etiology

In more than 95% of cases, a specific underlying cause of hypertension cannot be found. Such patients are said to have essential hypertension. The pathogenesis is not clearly understood. Many factors may contribute to its development, including renal dysfunction, peripheral resistance vessel tone, endothelial dysfunction, autonomic tone, insulin resistance and neurohumoral factors.

Definition of hypertension		
Category	**Systolic BP(mmHg)**	**Diastolic BP(mmHg)**
BP		
Optimal	< 120	< 80
Normal	< 130	85
High normal	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥ 180	> 110
Isolated systolic hypertension		
Grade 1	140–159	< 90
Grade 2	≥ 160	< 90

Hypertension is more common in some ethnic groups, particularly African Americans and Japanese, and approximately 40–60% is explained by genetic factors. Important environmental factors include a high salt intake, heavy consumption of alcohol, obesity, lack of exercise and impaired intrauterine growth. There is little evidence that ‘stress’ causes hypertension.

In about 5% of cases, hypertension can be shown to be a consequence of a specific disease or abnormality leading to sodium retention and/or peripheral vasoconstriction.

Approach to newly diagnosed hypertension

Hypertension is predominantly an asymptomatic condition and the diagnosis

is usually made at routine examination or when a complication arises. A BP check is advisable every 5 years in adults.

The objectives of the initial evaluation of a patient with high BP readings are:

• to obtain accurate, representative BP measurements

• to identify contributory factors and any underlying cause (secondary hypertension)

• to assess other risk factors and quantify cardiovascular risk

• to detect any complications (target organ damage) that are already present

• to identify comorbidity that may influence the choice of antihypertensive therapy.

These goals are attained by a careful history, clinical examination and some simple investigations.

History

Family history, lifestyle (exercise, salt intake, smoking habit) and other risk factors should be recorded. A careful history will identify those patients with drug- or alcohol-induced hypertension and may elicit the symptoms of other causes of secondary hypertension, such as phaeochromocytoma (paroxysmal headache, palpitation and sweating,) or complications such as coronary artery disease (e.g. angina, breathlessness).

Examination

Radio-femoral delay (coarctation of the aorta), enlarged kidneys (polycystic kidney

disease), abdominal bruits (renal artery stenosis) and the characteristic facies and habitus of Cushing's syndrome are all examples of physical signs that may help to identify causes of secondary hypertension. Examination may also reveal features of important risk factors, such as central obesity and hyperlipidaemia (tendon xanthomas and so on). Most abnormal signs are due to the complications of hypertension.

Non-specific findings may include left ventricular hypertrophy (apical heave), accentuation of the aortic component of the second heart sound, and a fourth heart sound. The optic fundi are often abnormal and there may be evidence of generalized atheroma or specific complications, such as aortic aneurysm or peripheral vascular disease.

Target organ damage

The adverse effects of hypertension on the organs can often be detected clinically.

Blood vessels

In larger arteries (> 1 mm in diameter), the internal elastic lamina is thickened, smooth muscle is hypertrophied and fibrous tissue is deposited. The vessels dilate and become tortuous, and their walls become less compliant. In smaller arteries

(< 1 mm), hyaline arteriosclerosis occurs in the wall, the lumen narrows and aneurysms may develop. Widespread atheroma develops and may lead to coronary and cerebrovascular disease, particularly if other risk factors (e.g. smoking, hyperlipidaemia, diabetes) are present.

These structural changes in the vasculature often perpetuate and aggravate hypertension by increasing peripheral vascular resistance and reducing renal blood flow, thereby activating the renin–angiotensin–aldosterone axis.

Hypertension is a major risk factor in the pathogenesis of aortic aneurysm and aortic dissection.

Central nervous system

Stroke is a common complication of hypertension and may be due to cerebral haemorrhage or infarction. Carotid atheroma and TIAs are more common in hypertensive patients. Subarachnoid haemorrhage is also associated with hypertension.

Hypertensive encephalopathy is a rare condition characterised by high BP and neurological symptoms, including transient disturbances of speech or vision, paraesthesiae, disorientation, fits and loss of consciousness. Papilloedema is common. A CT scan of the brain often shows haemorrhage in and around the basal ganglia; however, the neurological deficit is usually reversible if the hypertension is properly controlled.

Retina

The optic fundi reveal a gradation of changes linked to the severity of hypertension; fundoscopy can, therefore, provide an indication of the arteriolar damage occurring elsewhere.

'Cotton wool' exudates are associated with retinal ischaemia or infarction, and fade in a few weeks. 'Hard' exudates (small, white, dense deposits of lipid) and microaneurysms ('dot' haemorrhages) are more characteristic of diabetic retinopathy. Hypertension is also associated with central retinal vein thrombosis.

Heart

The excess cardiac mortality and morbidity associated with hypertension are largely due to a higher incidence of coronary artery disease. High BP places a pressure load on the heart and may lead to left ventricular hypertrophy with a forceful apex beat and fourth heart sound. ECG or echocardiographic evidence of left ventricular hypertrophy is highly predictive of cardiovascular complications and therefore particularly useful in risk assessment.

Atrial fibrillation is common and may be due to diastolic dysfunction caused by left ventricular hypertrophy or the effects of coronary artery disease.

Severe hypertension can cause left ventricular failure in the absence of coronary artery disease, particularly when renal function, and therefore sodium excretion, are impaired.

Kidneys

Long-standing hypertension may cause proteinuria and progressive renal failure by damaging the renal vasculature.

'Malignant' or 'accelerated' phase of hypertension

This rare condition may complicate hypertension of any aetiology and is characterised by accelerated microvascular damage with necrosis in the walls of small arteries and arterioles ('fibrinoid necrosis') and by intravascular thrombosis. The diagnosis is based on evidence of high BP and rapidly progressive end organ damage, such as retinopathy (grade 3 or 4), renal dysfunction (especially proteinuria) and/or hypertensive encephalopathy (see above). Left ventricular failure may occur and, if this is untreated, death occurs within months.

Investigations

All hypertensive patients should undergo a limited number of investigations. Additional investigations are appropriate in selected patients.

Hypertension: investigation of all patients

• Urinalysis for blood, protein and glucose
• Blood urea, electrolytes and creatinine

N.B. Hypokalaemic alkalosis may indicate primary hyperaldosteronism but is usually due to diuretic therapy

• Blood glucose
• Serum total and HDL cholesterol
• Thyroid function tests
• 12-lead ECG (left ventricular hypertrophy, coronary arterydisease)

Hypertension: investigation of selected Patients

• Chest X-ray: to detect cardiomegaly, heart failure, coarctation of the aorta
• Ambulatory BP recording: to assess borderline or 'white coat' hypertension
• Echocardiogram: to detect or quantify left ventricular hypertrophy
• Renal ultrasound: to detect possible renal disease
• Renal angiography: to detect or confirm presence of renal artery stenosis
• Urinary catecholamines: to detect possible phaeochromocytoma
• Urinary cortisol and dexamethasone suppression test: to detect possible Cushing's syndrome
• Plasma renin activity and aldosterone: to detect possible primary aldosteronism

Management

Quantification of cardiovascular risk

The sole objective of antihypertensive therapy is to reduce the incidence of adverse cardiovascular events, particularly coronary artery disease, stroke and heart failure. Randomised controlled trials have demonstrated that antihypertensive therapy can reduce the incidence of stroke and, to a lesser extent, coronary artery disease. The relative benefits (approximately 30% reduction in risk of stroke and 20% reduction in

risk of coronary artery disease) are similar in all patient groups, so the absolute benefit of treatment (total number of events prevented) is greatest in those at highest risk. For example, to extrapolate from the Medical Research Council (MRC) Mild Hypertension Trial (1985), 566 young patients would have to be treated with bendroflumethiazide for 1 year to prevent 1 stroke, while in the MRC trial of antihypertensive treatment in the elderly (1992), 1 stroke was prevented for every 286 patients treated for 1 year.

A formal estimate of absolute cardiovascular risk, which takes account of all the relevant risk factors, may help to determine whether the likely benefits of therapy will outweigh its costs and hazards. A variety of risk algorithms are available for this purpose. Most of the excess morbidity and mortality associated with hypertension is attributable to coronary artery disease and many treatment guidelines are therefore based on estimates of the 10-year coronary artery disease risk. Total cardiovascular risk can be estimated by multiplying coronary artery disease risk by 4/3 (i.e. if coronary artery disease risk is 30%, cardiovascular risk is 40%). The value of this approach can be illustrated by comparing the two hypothetical cases on page 582.

Threshold for intervention

Systolic BP and diastolic BP are both powerful predictors of cardiovascular risk. The British Hypertension Society management guidelines therefore utilise both readings, and treatment should be initiated if they exceed the given threshold.

Patients with diabetes or cardiovascular disease are at particularly high risk and the threshold for initiating antihypertensive therapy is therefore lower ($\geq$ 140/90 mmHg) in these patient groups. The thresholds for treatment in the elderly are the same as for younger patients.

Treatment targets

The optimum BP for reduction of major cardiovascular events has been found to be 139/83 mmHg, and even lower in patients with diabetes mellitus. Moreover, reducing BP below this level causes no harm. The targets suggested by the British Hypertension Society are ambitious. Primary care strategies have been devised to improve screening and detection of hypertension that, in the past, remained undetected in up to half of affected individuals. Application of new guidelines should help establish patients on appropriate treatment, and allow step-up if lifestyle modification and first-line drug therapy fail to control patients' BP.

Patients taking antihypertensive therapy require follow-up at 3-monthly intervals to monitor BP, minimize side-effects and reinforce lifestyle advice.

Non-drug therapy

Appropriate lifestyle measures may obviate the need for drug therapy in patients with borderline hypertension, reduce the dose and/or the number of drugs required in patients with established hypertension, and directly reduce cardiovascular risk.

Correcting obesity, reducing alcohol intake, restricting salt intake, taking regular physical exercise and increasing consumption of fruit and vegetables can all

lower BP. Moreover, quitting smoking, eating oily fish and adopting a diet that is low in saturated fat may produce further reductions in cardiovascular risk.

Antihypertensive drugs

Thiazide and other diuretics. The mechanism of action of these drugs is incompletely understood and it may take up to a month for the maximum effect to be observed. An appropriate daily dose is 2.5 mg bendroflumethiazide or 0.5 mg cyclopenthiazide. More potent loop diuretics, such as furosemide (40 mg daily) or bumetanide (1 mg daily), have few advantages over thiazides in the treatment of hypertension, unless there is substantial renal impairment or they are used in conjunction with an ACE inhibitor.

ACE inhibitors. ACE inhibitors (e.g. enalapril 20 mg daily, ramipril 5–10 mg daily or lisinopril 10–40 mg daily) inhibit the conversion of angiotensin I to angiotensin II and are usually well tolerated. They should be used with particular care in patients with impaired renal function or renal artery stenosis because they can reduce the filtration pressure in the glomeruli and precipitate renal failure. Electrolytes and creatinine should be checked before and 1–2 weeks after commencing therapy. Side-effects include first-dose hypotension, cough, rash, hyperkalaemia and renal dysfunction.

Angiotensin receptor blockers. Angiotensin receptor blockers (e.g. irbesartan 150–300 mg daily, valsartan 40–160 mg daily) block the angiotensin II type I receptor and have similar effects to ACE inhibitors; however, they do not cause cough and are better tolerated.

Calcium channel antagonists. The dihydropyridines (e.g. amlodipine 5–10 mg daily, nifedipine 30–90 mg daily) are effective and usually well-tolerated antihypertensive drugs that are particularly useful in older people. Side-effects include flushing, palpitations and fluid retention. The rate-limiting calcium channel antagonists (e.g. diltiazem 200–300 mg daily, verapamil 240 mg daily) can be useful when hypertension coexists with angina but they may cause bradycardia. The main sideeffect of verapamil is constipation.

Beta-blockers. These are no longer used as first-line antihypertensive therapy, except in patients with another indication for the drug (e.g. angina). Metoprolol (100–200 mg daily), atenolol (50–100 mg daily) and bisoprolol (5–10 mg daily) preferentially block cardiac β1-adrenoceptors, as opposed to the β2-adrenoceptors that mediate vasodilatation and bronchodilatation.

Labetalol and carvedilol. Labetalol (200 mg–2.4 g daily in divided doses) and carvedilol (6.25–25 mg twice daily) are combined β- and α-adrenoceptor antagonists which are sometimes more effective than pure β-blockers. Labetalol can be used as an infusion in malignant phase hypertension (see below).

Other drugs. A variety of vasodilators may be used. These include the α1-adrenoceptor antagonists (α-blockers), such as prazosin (0.5–20 mg daily in divided doses), indoramin (25–100 mg twice daily) and doxazosin (1–16 mg daily), and drugs that act directly on vascular smooth muscle, such as hydralazine (25–100 mg twice daily) and minoxidil (10–50 mg daily). Side-effects include first-dose and postural hypotension, headache, tachycardia and fluid retention. Minoxidil also causes increased facial hair and is therefore unsuitable for female patients.

Choice of antihypertensive drug

Trials that have compared thiazides, calcium antagonists, ACE inhibitors and angiotensin receptor blockers have not shown consistent differences in outcome, efficacy, side-effects or quality of life. Beta-blockers, which previously featured as first-line therapy in guidelines, have a weaker evidence base. The choice of antihypertensive therapy is initially dictated by the patient's age and ethnic background, although cost and convenience will influence the exact drug and preparation used. Response to initial therapy and side-effects guides subsequent treatment. Comorbid conditions also have an influence on initial drug selection; for example, a β-blocker might be the most appropriate treatment for a patient with angina. Thiazide diuretics and dihydropyridine calcium channel antagonists are the most suitable drugs for treatment in older people.

Although some patients can be treated with a single antihypertensive drug, a combination of drugs is often required to achieve optimal BP control. Combination therapy may be desirable for other reasons; for example, low-dose therapy with two drugs may produce fewer unwanted effects than treatment with the maximum dose of a single drug. Some drug combinations have complementary or synergistic actions; for example, thiazides increase activity of the renin– angiotensin system, while ACE inhibitors block it.

Emergency treatment of accelerated phase or malignant hypertension

In accelerated phase hypertension, lowering BP too quickly may compromise tissue perfusion (due to altered autoregulation) and can cause cerebral damage, including occipital blindness, and precipitate coronary or renal insufficiency. Even in the presence of cardiac failure or hypertensive encephalopathy, a controlled reduction to a level of about 150/90 mmHg over a period of 24–48 hours is ideal.

In most patients, it is possible to avoid parenteral therapy and bring BP under control with bed rest and oral drug therapy. Intravenous or intramuscular labetalol (2 mg/min to a maximum of 200 mg), intravenous glyceryl trinitrate (0.6–1.2 mg/hr), intramuscular hydralazine (5 or 10 mg aliquots repeated at halfhourly intervals) and intravenous sodium nitroprusside (0.3–1.0 μg/kg body weight/min) are all effective but require careful supervision, preferably in a highdependency unit.

Refractory hypertension

The common causes of treatment failure in hypertension are non-adherence to drug therapy, inadequate therapy, and failure to recognise an underlying cause, such as \renal artery stenosis or phaeochromocytoma; of these, the first is by far the most prevalent. There is no easy solution to compliance problems but simple treatment regimens, attempts to improve rapport with the patient and careful supervision may all help.

Adjuvant drug therapy

• *Aspirin*. Antiplatelet therapy is a powerful means of reducing cardiovascular

risk but may cause bleeding, particularly intracerebral haemorrhage, in a small number of patients. The benefits are thought to outweigh the risks in hypertensive patients aged 50 years or over who have wellcontrolled BP and either target organ damage, diabetes or a 10-year coronary artery disease risk of at least 15% (or 10-year cardiovascular disease risk of at least 20%).

• *Statins*. Treating hyperlipidaemia can produce a substantial reduction in cardiovascular risk. These drugs are strongly indicated in patients who have established vascular disease, or hypertension with a high (at least 20% in 10 years) risk of developing cardiovascular disease

General material and educational and methodological support of the lecture:

- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for the self-control

1. Define essential arterial hypertension
2. Define of hypertensive crisis
3. Give classification of essential arterial hypertension
4. Give a list of risk factors of essential arterial hypertension
5. Describe the main pathogenetic mechanisms of essential arterial hypertension
6. Identify the main clinical syndromes essential arterial hypertension
7. Determination of clinical features of essential arterial hypertension
8. Give a list of laboratory diagnostic criteria for essential arterial hypertension
9. Define a treatment program for essential arterial hypertension
10. Describe prevention measures and determine the forecast for essential arterial hypertension

List of used sources:

1 . http://www.asco.org/practice-guidelines/quality-guidelines/guidelines
2. https://www.asn-online.org/education/training/fellows/educational-resources.aspx#Guidelines
3. www.brit-thoracic.org.uk/standards-of-care/guidelines
4. https://cprguidelines.eu/
5.Harrison's Endocrinology. Ed. by J. Larry Jameson, Mc Graw – Hill., New York, Chicago,Toronto. e.a. 5rd edition, 2019. - 608 p.
6. Clinical Medicine. Adam Feather MBBS, FRCP, FAcadMEd. David Randall MA, MRCP. Mona Waterhouse MA (Oxon), MRCP. London New York Oxford Philadelphia St Louis Sydney 2021

Lecture № 2

Topic: Atherosclerosis

Actuality of theme: Atherosclerosis, a disease of the large arteries, is the primary cause of heart disease and stroke. In westernized societies, it is the underlying cause of about 50% of all deaths. Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis. Progress in defining the cellular and molecular interactions involved, however, has been hindered by the disease's etiological complexity. Over the past decade, the availability of new investigative tools, including genetically modified mouse models of disease, has resulted in a clearer understanding of the molecular mechanisms that connect altered cholesterol metabolism and other risk factors to the development of atherosclerotic plaque. It is now clear that atherosclerosis is not simply an inevitable degenerative consequence of ageing, but rather a chronic inflammatory condition that can be converted into an acute clinical event by plaque rupture and thrombosis.

Goal: explain the essence of the atherosclerotic process, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: lipids, low density lipoproteins, high density lipoproteins, triglycerides, endothelial damaging, ischemic heart disease, lipid lowering medications

Lecture plan and organizational structure

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: Relevance of the topic Definition Classification Etiology and main links of pathogenesis Symptoms and signs Diagnostic criteria Main syndromes and differential diagnosis Criteria for the severity of disease Treatment	 II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

	Prevention	II II		
III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Atherosclerosis, chronic disease caused by the deposition of fats, cholesterol, calcium, and other substances in the innermost layer of endothelium of the large and medium-sized arteries. Atherosclerosis is the most common arterial abnormality characterized as arteriosclerosis, which is defined by the loss of arterial elasticity due to vessel thickening and stiffening. The precise mechanisms of atherosclerosis are not completely understood, but there is evidence that in some people the condition can begin in childhood with the formation of tiny "fatty streaks," or streaks of fat deposition, in the arteries. As the endothelium is infiltrated by more and more fatty materials—primarily low-density lipoproteins (LDLs), protein-lipid complexes that serve as a vehicle for delivering cholesterol to the body—immune cells called macrophages are drawn to the site to scavenge the materials. When filled with lipids the macrophages become known as "foam cells," which later die and accumulate in the endothelial lining. Other materials are also deposited in the lining, including salts of calcium and other minerals, smooth muscle cells, and cellular debris of varying composition. This causes the initially tiny lesions to enlarge and thicken to form atheromas, or atherosclerotic plaques. These plaques may narrow the vessel channel, interfering with the flow of blood. Endothelial injury, either as a result of lipid deposition or as a result of another cause, may also be accompanied by the formation of fibrous caps of scar tissue. These areas of scar tissue make the vessel walls less elastic, with one consequence being an increase in blood pressure. Thick plaques that severely occlude an artery can significantly decrease the flow of blood to vascular beds in tissues served by the artery, thereby causing severe tissue damage. In addition, a disturbance to the endothelium may result in the formation of a blood clot (thrombus) at the site of a plaque, likewise obstructing the channel or breaking loose from the site and causing a catastrophic blockage elsewhere.

Atherosclerotic lesions frequently are found in the aorta and in large aortic branches. They are also prevalent in the coronary arteries, where the condition is called coronary heart disease (also called coronary artery disease or ischemic heart disease). When atherosclerosis affects the coronary arteries, which bring oxygen-rich blood to the heart muscle, it can decrease the supply of blood to the heart muscle and result in chest pain known as angina pectoris. The complete occlusion of one or more coronary arteries can cause the death of a section of the heart muscle (myocardial infarction, or heart attack). Atherosclerotic lesions of the cerebral vessels may lead to formation of blood clots and stroke.

A family history of cardiovascular disease, smoking, stress, obesity, and high blood cholesterol levels, particularly in association with LDLs, are among the factors that contribute to an increased risk of developing atherosclerosis. Men develop atherosclerosis more often than women, and individuals with diabetes mellitus have a significantly higher incidence of the disease.

Causes

Atherosclerosis develops from low-density lipoprotein molecules (LDL) becoming oxidized (ldl-ox) by free radicals, particularly reactive oxygen species (ROS). When oxidized LDL comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by oxidized LDL. The LDL molecule is globular shaped with a hollow core to carry cholesterol throughout the body. Cholesterol can move in the bloodstream only by being transported by lipoproteins.

The body's immune system responds to the damage to the artery wall caused by oxidized LDL by sending specialized white blood cells (macrophages and T-lymphocytes) to absorb the oxidized-LDL forming specialized foam cells. Unfortunately, these white blood cells are not able to process the oxidized-LDL, and ultimately grow then rupture, depositing a greater amount of oxidized cholesterol into the artery wall. This triggers more white blood cells, continuing the cycle.

Eventually, the artery becomes inflamed. The cholesterol plaque causes the muscle cells to enlarge and form a hard cover over the affected area. This hard cover is what causes a narrowing of the artery, reduces the blood flow and increases blood pressure.

Some researchers believe that atherosclerosis may be caused by an infection of the vascular smooth muscle cells. Chickens, for example, develop atherosclerosis when infected with the Marek's disease herpesvirus. Herpesvirus infection of arterial smooth muscle cells has been shown to cause cholesteryl ester (CE) accumulation. Cholesteryl ester accumulation is associated with atherosclerosis.

Also, cytomegalovirus (CMV) infection is associated with cardiovascular diseases.

Pathophysiology

Atherogenesis is the developmental process of atheromatous plaques. It is characterized by a remodeling of arteries involving the concomitant accumulation of fatty substances called plaques. One recent theory suggests that, for unknown reasons, leukocytes, such as monocytes or basophils, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to formation of atheromatous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media. The bulk of these lesions is made of excess fat, collagen, and elastin. At first, as the plaques grow, only wall thickening occurs without any narrowing, stenosis of the artery opening, called the lumen; stenosis is a late event, which may never occur and is often the result of repeated plaque rupture and healing responses, not just the atherosclerosis process by itself.

Cellular

Micrograph of an artery that supplies the heart with significant atherosclerosis and marked luminal narrowing. Masson's trichrome.

The first step of atherogenesis is the development of so called "fatty streaks",

which are small sub-endothelial deposits of monocyte-derived macrophages. The primary documented driver of this process is oxidized Lipoprotein particles within the wall, beneath the endothelial cells, though upper normal or elevated concentrations of blood glucose also plays a major role and not all factors are fully understood. Fatty streaks may appear and disappear.

Low Density Lipoprotein particles in blood plasma, when they invade the endothelium and become oxidized creates a risk for cardiovascular disease. A complex set of biochemical reactions regulates the oxidation of LDL, chiefly stimulated by presence of enzymes, e.g. Lp-LpA2 and free radicals in the endothelium or blood vessel lining.

The initial damage to the blood vessel wall results in a "call for help," an inflammatory response. Monocytes (a type of white blood cell) enter the artery wall from the bloodstream, with platelets adhering to the area of insult. This may be promoted by redox signaling induction of factors such as VCAM-1, which recruit circulating monocytes. The monocytes differentiate macrophages, which ingest oxidizedLDL, slowly turning into large "foam cells" – so-described because of their changed appearance resulting from the numerous internal cytoplasmic vesicles and resulting high lipid content. Under the microscope, the lesion now appears as a fatty streak. Foam cells eventually die, and further propagate the inflammatory process. There is also smooth muscle proliferation and migration from tunica media to intima responding to cytokines secreted by damaged endothelial cells. This would cause the formation of a fibrous capsule covering the fatty streak.

Calcification and lipids

Intracellular microcalcifications form within vascular smooth muscle cells of the surrounding muscular layer, specifically in the muscle cells adjacent to the atheromas. In time, as cells die, this leads to extracellular calcium deposits between the muscular wall and outer portion of the atheromatous plaques. A similar form of an intramural calcification, presenting the picture of an early phase of arteriosclerosis, appears to be induced by a number of drugs that have an antiproliferative mechanism of action.

Cholesterol is delivered into the vessel wall by cholesterol-containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process. The process is worsened if there is insufficient high-density lipoprotein (HDL), the lipoprotein particle that removes cholesterol from tissues and carries it back to the liver.

The foam cells and platelets encourage the migration and proliferation of smooth muscle cells, which in turn ingest lipids, become replaced by collagen and transform into foam cells themselves. A protective fibrous cap normally forms between the fatty deposits and the artery lining (the intima).

These capped fatty deposits (now called 'atheromas') produce enzymes that cause the artery to enlarge over time. As long as the artery enlarges sufficiently to compensate for the extra thickness of the atheroma, then no narrowing ("stenosis") of the opening ("lumen") occurs. The artery becomes expanded with an egg-shaped cross-section, still with a circular opening. If the enlargement is beyond proportion to the atheroma thickness, then an aneurysm is created.

Visible features

Although arteries are not typically studied microscopically, two plaque types can be distinguished:

The fibro-lipid (fibro-fatty) plaque is characterized by an accumulation of lipid-laden cells underneath the intima of the arteries, typically without narrowing the lumen due to compensatory expansion of the bounding muscular layer of the artery wall. Beneath the endothelium there is a "fibrous cap" covering the atheromatous "core" of the plaque. The core consists of lipid-laden cells (macrophages and smooth muscle cells) with elevated tissue cholesterol and cholesterol ester content, fibrin, proteoglycans, collagen, elastin, and cellular debris. In advanced plaques, the central core of the plaque usually contains extracellular cholesterol deposits (released from dead cells), which form areas of cholesterol crystals with empty, needle-like clefts. At the periphery of the plaque are younger "foamy" cells and capillaries. These plaques usually produce the most damage to the individual when they rupture.

The fibrous plaque is also localized under the intima, within the wall of the artery resulting in thickening and expansion of the wall and, sometimes, spotty localized narrowing of the lumen with some atrophy of the muscular layer. The fibrous plaque contains collagen fibers (eosinophilic), precipitates of calcium (hematoxylinophilic) and, rarely, lipid-laden cells.

In effect, the muscular portion of the artery wall forms small aneurysms just large enough to hold the atheroma that are present. The muscular portion of artery walls usually remain strong, even after they have remodeled to compensate for the atheromatous plaques.

However, atheromas within the vessel wall are soft and fragile with little elasticity. Arteries constantly expand and contract with each heartbeat, i.e., the pulse. In addition, the calcification deposits between the outer portion of the atheroma and the muscular wall, as they progress, lead to a loss of elasticity and stiffening of the artery as a whole.

The calcification deposits, after they have become sufficiently advanced, are partially visible on coronary artery computed tomography or electron beam tomography (EBT) as rings of increased radiographic density, forming halos around the outer edges of the atheromatous plaques, within the artery wall. On CT, >130 units on the Hounsfield scale (some argue for 90 units) has been the radiographic density usually accepted as clearly representing tissue calcification within arteries. These deposits demonstrate unequivocal evidence of the disease, relatively advanced, even though the lumen of the artery is often still normal by angiographic or intravascular ultrasound.

In days gone by the lateral chest x-ray (demonstrating greater opacity in the aortic arch and descending aorta than the thoracic spine) gave an indication to the degree of calcified plaque burden a patient had. This has been known as Piper's sign and can often be seen in elderly persons particularly those with concomitant osteoporosis.

Rupture and stenosis

Although the disease process tends to be slowly progressive over decades, it usually remains asymptomatic until an atheroma ulcerates which leads to immediate blood clotting at the site of atheroma ulcer. This triggers a cascade of events that leads to clot enlargement which may quickly obstruct the lumen (opening) of the artery itself.

A complete blockage leads to ischemia of the myocardial (heart) muscle and damage. This process is the myocardial infarction or "heart attack."

If the heart attack is not fatal, fibrous organization of the clot within the lumen ensues, covering the rupture but also producing stenosis or closure of the lumen, or over time and after repeated ruptures, resulting in a persistent, usually localized stenosis or blockage of the artery lumen. Stenosis can be slowly progressive, whereas plaque ulceration is a sudden event that occurs specifically in atheromas with thinner/weaker fibrous caps that have become "unstable."

Repeated plaque ruptures, ones not resulting in total lumen closure, combined with the clot patch over the rupture and healing response to stabilize the clot, is the process that produces most stenoses over time. The stenotic areas tend to become more stable, despite increased flow velocities at these narrowings. Most major blood-flow-stopping events occur at large plaques, which, prior to their rupture, produced very little if any stenosis.

From clinical trials, 20% is the average stenosis at plaques that subsequently rupture with resulting complete artery closure. Most severe clinical events do not occur at plaques that produce high-grade stenosis. From clinical trials, only 14% of heart attacks occur from artery closure at plaques producing a 75% or greater stenosis prior to the vessel closing.

If the fibrous cap separating a soft atheroma from the bloodstream within the artery ruptures, tissue fragments are exposed and released, and blood enters the atheroma within the wall and sometimes results in a sudden expansion of the atheroma size. Tissue fragments are very clot-promoting, containing collagen and tissue factor; they activate platelets and activate the system of coagulation. The result is the formation of a thrombus (blood clot) overlying the atheroma, which obstructs blood flow acutely. With the obstruction of blood flow, downstream tissues are starved of oxygen and nutrients. If this is the myocardium (heart muscle), angina (cardiac chest pain) or myocardial infarction (heart attack) develops.

Signs and symptoms

Atherosclerosis typically begins in early adolescence, and is usually found in most major arteries, yet is asymptomatic and not detected by most diagnostic methods during life. Atheroma in arm, or more often in leg arteries, which produces decreased blood flow is called peripheral artery occlusive disease (PAOD).

According to United States data for the year 2004, for about 65% of men and 47% of women, the first symptom of atherosclerotic cardiovascular disease is heart attack or sudden cardiac death (death within one hour of onset of the symptom).

Most artery flow disrupting events occur at locations with less than 50% lumen narrowing (~20% stenosis is average).

Cardiac stress testing, traditionally the most commonly performed non-invasive testing method for blood flow limitations, in general, detects only lumen narrowing of ~75% or greater, although some physicians claim that nuclear stress methods can detect as little as 50%.

Diagnosis

Microphotography of arterial wall with calcified (violet colour) atherosclerotic plaque.

Areas of severe narrowing, stenosis, detectable by angiography, and to a lesser extent "stress testing" have long been the focus of human diagnostic techniques for cardiovascular disease, in general. However, these methods focus on detecting only severe narrowing, not the underlying atherosclerosis disease. As demonstrated by human clinical studies, most severe events occur in locations with heavy plaque, yet little or no lumen narrowing present before debilitating events suddenly occur. Plaque rupture can lead to artery lumen occlusion within seconds to minutes, and potential permanent debility and sometimes sudden death.

Plaques that have ruptured are called complicated plaques. The lipid matrix breaks through the thinning collagen gap and when the lipids come in contact with the blood, clotting occurs. After rupture the platelet adhesion causes the clotting cascade to contact with the lipid pool causing a thrombus to form. This thrombus will eventually grow and travel throughout the body. The thrombus will travel through different arteries and veins and eventually become lodged in an area that narrows. Once the area is blocked, blood and oxygen will not be able to supply the vessels and will cause death of cells and lead to necrosis and poisoning. Serious complicated plaques can cause death of organ tissues, causing serious complications to that organ system.

Greater than 75% lumen stenosis used to be considered by cardiologists as the hallmark of clinically significant disease because it is typically only at this severity of narrowing of the larger heart arteries that recurring episodes of angina and detectable abnormalities by stress testing methods are seen. However, clinical trials have shown that only about 14% of clinically-debilitating events occur at locations with this, or greater severity of stenosis. The majority of events occur due to atheroma plaque rupture at areas without narrowing sufficient enough to produce any angina or stress test abnormalities. Thus, since the later-1990s, greater attention is being focused on the "vulnerable plaque."

Though any artery in the body can be involved, usually only severe narrowing or obstruction of some arteries, those that supply more critically-important organs are recognized. Obstruction of arteries supplying the heart muscle result in a heart attack. Obstruction of arteries supplying the brain result in a stroke. These events are life-changing, and often result in irreversible loss of function because lost heart muscle and brain cells do not grow back to any significant extent, typically less than 2%.

Over the last couple of decades, methods other than angiography and stress-testing have been increasingly developed as ways to better detect atherosclerotic disease before it becomes symptomatic. These have included both (a) anatomic detection methods and (b) physiologic measurement methods.

Assessment of ASCVD Risk

Assessment of ASCVD risk is the foundation of primary prevention. For those aged 20-39 years, it is reasonable to measure traditional risk factors every 4-6 years to identify major factors (e.g., tobacco, dyslipidemia, family history of premature ASCVD, chronic inflammatory diseases, hypertension, or type 2 diabetes mellitus [T2DM]) that provide rationale for optimizing lifestyle and tracking risk factor progression and need for treatment. For adults aged 20-39 years and those aged 40-59 years who are not already at elevated (≥7.5%) 10-year risk, estimating a lifetime or 30-year risk for ASCVD may be considered (ASCVD Risk Estimator Plus). For those aged 20-59 years

not at high short-term risk, the 30-year and lifetime risk would be reasons for a communication strategy for reinforcing adherence to lifestyle recommendations and for some drug therapy (e.g., familial hypercholesterolemia, hypertension, prediabetes, family history of premature ASCVD with dyslipidemia or elevated lipoprotein [a] Lp[a]).

Estimating Risk of ASCVD

Electronic and paper chart risk estimators are available that utilize population-based and clinical trial outcomes with the goal of matching need and intensity of preventive therapies to absolute risk (generally 10 years) for ASCVD events. The guideline suggests the race- and sex-specific Pooled Cohort Equation (PCE) (ASCVD Risk Estimator Plus) to estimate 10-year ASCVD risk for asymptomatic adults aged 40-79 years. Adults should be categorized into low (<5%), borderline (5 to <7.5%), intermediate (≥7.5 to <20%), or high (≥20%) 10-year risk. The PCEs are best validated among non-Hispanic whites and non-Hispanic blacks living in the United States. In other race/ethnic groups and some non-US populations, the PCE may over- or under-estimate risk (e.g., HIV infection, chronic inflammatory or autoimmune disease, and low socioeconomic levels). Consideration should be given to use of other risk prediction tools if validated in a population with similar characteristics. Examples include the general Framingham CVD risk score, Reynolds risk score, SCORE, and QRISK/JBS3 tools. Among borderline and intermediate-risk adults, one may consider additional individual "risk-enhancing" clinical factors that can be used to revise the 10-year ASCVD risk estimate. For initiating or intensifying statin therapy, include: family history of premature ASCVD (men <55 years, women <65 years); low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dl or non-high-density lipoprotein cholesterol (non-HDL-C) ≥190 mg/dl; chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2); metabolic syndrome; pre-eclampsia and premature menopause (<40 years); inflammatory diseases including rheumatoid arthritis, lupus, psoriasis, HIV; South Asian ancestry; biomarkers including fasting triglycerides ≥175 mg/dl, Lp(a) ≥50 mg/dl, high-sensitivity C-reactive protein ≥2 mg/L, apolipoprotein B >130 mg/dl, and ankle-brachial index (ABI) <0.9. After considering these clinically available risk-enhancing factors, if there is still uncertainty about the reliability of the risk estimate for individuals in the borderline or intermediate-risk categories, further testing to document subclinical coronary atherosclerosis with computed tomography-derived coronary artery calcium score (CACs) is reasonable to more accurately reclassify the risk estimate upward or downward.

For persons at intermediate predicted risk (≥7.5 to <20%) by the PCE or borderline (5 to <7.5%) predicted risk, CACs helps refine risk assessment. CACs can re-classify risk upward (particularly when score is ≥100 or ≥75th age/sex/race percentile) or downward (if CACs = 0), which is not uncommon, particularly in men <50 and women <60 years. In MESA (Multi-Ethnic Study of Atherosclerosis), the CACs was strongly associated with 10-year ASCVD risk in a graded fashion across age, sex, and race/ethnic groups, and independent of traditional risk factors. CAC may refine ASCVD risk estimates among lower-risk women (<7.5% 10-year risk), younger adults (<45 years), and older adults (≥75 years), but more data are needed to support its use in these sub-

groups. A CACs = 0 identifies individuals at lower risk of ASCVD events and mortality over a ≥10-year period, who appear to derive little or no benefit from statins and for which drug interventions can be delayed. The absence of CAC does not rule out noncalcified plaque, and clinical judgment about risk should prevail. CAC might also be considered in refining risk for selected low-risk adults (<5% 10-year risk) such as those with a strong family history of premature coronary heart disease (CHD). There are Internet-available risk estimation tools (MESA and ASTROCHARM), which incorporate both risk factors and CAC for estimating 10-year CHD or ASCVD risk, respectively. CAC measurement is not intended as a "screening" test for all, but rather is a decision aid in select adults to facilitate the clinician-patient risk discussion.

Nutrition

Dietary patterns associated with CVD mortality include—sugar, low-calorie sweeteners, high-carbohydrate diets, low-carbohydrate diets, refined grains, trans fat, saturated fat, sodium, red meat, and processed red meat (such as bacon, salami, ham, hot dogs, and sausage). All adults should consume a healthy plant-based or Mediterranean-like diet high in vegetables, fruits, nuts, whole grains, lean vegetable or animal protein (preferably fish), and vegetable fiber, which has been shown to lower the risk of all-cause mortality compared to control or standard diet. Longstanding dietary patterns that focus on low intake of carbohydrates and a high intake of animal fat and protein as well as high carbohydrate diets are associated with increased cardiac and noncardiac mortality. The increased availability of affordable, palatable, and high-calorie foods along with decreased physical demands of many jobs have fueled the epidemic of obesity and the consequent increases in hypertension and T2DM.

Obesity

Adults diagnosed as obese (body mass index [BMI] ≥30 kg/m^2) or overweight (BMI 25-29.9 kg/m^2) are at increased risk of ASCVD, heart failure, and atrial fibrillation compared with those of a normal weight. Obese and overweight adults are advised to participate in comprehensive lifestyle programs for 6 months that assist participants in adhering to a low-calorie diet (decrease by 500 kcal or 800-1500 kcal/day) and high levels of physical activity (200-300 minutes/week). Clinically meaningful weight loss (≥5% initial weight) is associated with improvement in blood pressure (BP), LDL-C, triglycerides, and glucose levels among obese or overweight individuals, and delays the development of T2DM. In addition to diet and exercise, FDA-approved pharmacologic therapies and bariatric surgery may have a role for weight loss in select patients.

Physical Activity

Despite the public health emphasis for regular exercise based on extensive observational data that aerobic physical activity lowers ASCVD, approximately 50% of adults in the United States do not meet minimum recommendations. There is a strong inverse dose-response relationship between the amount of moderate-to-vigorous physical activity and incident ASCVD events and mortality. Adults should engage in at least 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity physical activity including resistance exercise.

Diabetes mellitus

T2DM, defined as a hemoglobin A1c (HbA1c) >6.5%, is a metabolic disorder characterized by insulin resistance leading to hyperglycemia. The development and

progression are heavily influenced by dietary pattern, physical activity, and body weight. All with T2DM should undergo dietary counseling for a heart-healthy diet that in T2DM lowers CVD events and CVD mortality. Among options include the Mediterranean, DASH, and vegetarian/vegan diets that achieve weight loss and improve glycemic control. At least 150 minutes/week of moderate to vigorous physical activity (aerobic and resistance) in T2DM lowers HbA1c about 0.7% with an additional similar decrease by weight loss. *Other risk factors should be identified and treated aggressively.* For younger individuals, or those with a mildly elevated HbA1c at the time of diagnosis of T2DM, clinicians can consider a trial of lifestyle therapies for 3-6 months before drug therapy.

First-line therapy to improve glycemic control and reduce CVD risk is metformin. Compared to lifestyle modifications, metformin resulted in a 32% reduction in micro- and macrovascular diabetes-related outcomes, a 39% reduction in myocardial infarction, and a 36% reduction in all-cause mortality. The goal is a HbA1c 6.5-7%. Several classes of medications have been shown to effectively lower blood glucose but may not affect ASCVD risk including the often-used sulfonylureas. Two classes of glucose-lowering medications have recently demonstrated a reduction in ASCVD events in adults with T2DM and ASCVD. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, weight, and BP and in randomized clinical trials, significant reduction in ASCVD events and heart failure. The majority of patients studied had established CVD at baseline, although limited data suggest this class of medications may be beneficial for primary prevention. The glucagon-like peptide-1 receptor (GLP-1R) agonists increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. GLP-1R agonists have been found to significantly reduce the risk of ASCVD events in adults with T2DM at high ASCVD risk. In patients with T2DM and additional risk factors for CVD, it may be reasonable to initiate these two classes of medications for primary prevention of CVD.

Lipids

Primary ASCVD prevention requires assessing risk factors beginning in childhood. For those <19 years of age with familial hypercholesterolemia, a statin is indicated. For young adults (ages 20-39 years), priority should be given to estimating lifetime risk and promoting a healthy lifestyle. Statin should be considered in those with a family history of premature ASCVD and LDL-C ≥160 mg/dl. ASCVD risk-enhancing factors, (see risk estimate section), should be considered in all patients.

Statin Treatment Recommendations

The following are guideline recommendations for statin treatment:

- Patients ages 20-75 years and LDL-C ≥190 mg/dl, use high-intensity statin without risk assessment.
- T2DM and age 40-75 years, use moderate-intensity statin and risk estimate to consider high-intensity statins. Risk-enhancers in diabetics include ≥10 years for T2DM and 20 years for type 1 DM, ≥30 mcg albumin/mg creatinine, eGFR<60 ml/min/1.73 m^2, retinopathy, neuropathy, ABI <0.9. In those with multiple ASCVD risk factors, consider high-intensity statin with aim of lowering LDL-C by 50% or more.

- Age >75 years, clinical assessment and risk discussion.
- Age 40-75 years and LDL-C ≥70 mg/dl and <190 mg/dl without diabetes, use the risk estimator that best fits the patient and risk-enhancing factors to decide intensity of statin.
  - Risk 5% to <7.5% (borderline risk). Risk discussion: if risk-enhancing factors are present, discuss moderate-intensity statin and consider coronary CACs in select cases.
  - Risk ≥7.5-20% (intermediate risk). Risk discussion: use moderate-intensity statins and increase to high-intensity with risk enhancers. Option of CACs to risk stratify if there is uncertainty about risk. If CAC = 0, can avoid statins and repeat CAC in the future (5-10 years), the exceptions being high-risk conditions such as diabetes, family history of premature CHD, and smoking. If CACs 1-100, it is reasonable to initiate moderate-intensity statin for persons ≥55 years. If CAC >100 or 75th percentile or higher, use statin at any age.
  - Risk ≥20% (high risk). Risk discussion to initiate high-intensity statin to reduce LDL-C by ≥50%.

  Both moderate- and high-intensity statin therapy reduce ASCVD risk, but a greater reduction in LDL-C is associated with a greater reduction in ASCVD outcomes. The dose response and tolerance should be assessed in about 6-8 weeks. If LDL-C reduction is adequate (≥30% reduction with intermediate- and 50% with high-intensity statins), regular interval monitoring of risk factors and compliance with statin therapy are necessary to determine adherence and adequacy of effect (about 1 year). For patients aged >75 years, assessment of risk status and a clinician-patient risk discussion are needed to decide whether to continue or initiate statin treatment. The CACs may help refine ASCVD risk estimates among lower-risk women (<7.5%) and younger adults (<45 years), particularly in the setting of risk enhancers.

Hypertension

In the United States, hypertension accounts for more ASCVD deaths than any other modifiable risk factor. The prevalence of stage I hypertension defined as systolic BP (SBP) ≥130 or diastolic BP (DBP) ≥80 mm Hg among US adults is 46%, higher in blacks, Asians, and Hispanic Americans, and increases dramatically with increasing age. A meta-analysis of 61 prospective studies observed a log-linear association between SBP levels <115 to >180 mm Hg and DBP levels <75 to 105 mm Hg and risk of ASCVD. In that analysis, *20 mm Hg higher SBP and 10 mm Hg higher DBP were each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease.* An increased risk of ASCVD is associated with higher SBP and SBP has been reported across a broad age spectrum, from 30 to >80 years of age.

In adults with elevated or borderline hypertension (BP 120-129/<80 mm Hg) or hypertension, the initial recommendations include weight loss, heart-healthy diet (DASH or DASH Mediterranean), sodium restriction of 1000 mg reduction and optimal <1500 mg/d), diet rich in potassium with supplements as necessary, exercise as described including aerobic, isometric resistance (hand-grip), dynamic resistance (weights), and limited alcohol (men <3 and women <2 per day). In adults with stage I hypertension (BP 130-139/80-89 mm Hg) and estimated 10-year ASCVD risk of <10%, nonpharmacologic therapy is recommended. In those with a 10% or higher 10-year ASCVD

risk, use of BP-lowering medication is recommended with a BP target of <130/80 mm Hg including persons with chronic kidney disease and diabetes. A target of <130/80 mm Hg is also recommended for Stage 2 hypertension, defined as BP ≥140/90 mm Hg with nonpharmacological and BP-lowering medication.

Tobacco

Tobacco use is the leading preventable cause of disease, disability, and death in the United States. Smoking and smokeless tobacco (e.g., chewing tobacco) increases the risk for all-cause mortality and causal for ASCVD. Secondhand smoke is a cause of ASCVD and stroke, and almost one third of CHD deaths are attributable to smoking and exposure to secondhand smoke. Even low levels of smoking increase risks of acute myocardial infarction; thus, reducing the number of cigarettes per day does not totally eliminate risk. Electronic Nicotine Delivery Systems (ENDS), known as e-cigarettes and vaping, are a new class of tobacco products that emit aerosol containing fine and ultrafine particulates, nicotine, and toxic gases that may increase risk for CV and pulmonary diseases. Arrhythmias and hypertension with e-cigarette use have been reported. Chronic use is associated with persistent increases in oxidative stress and sympathetic stimulation in the healthy young.

All adults should be assessed at every visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit on every visit. Referral to specialists is helpful for both behavioral modification, nicotine replacement, and drug treatments. Amongst the treatments include varieties of nicotine replacement, the nicotine receptor blocker varenicline, and bupropion, an antidepressant.

Aspirin

For decades, low-dose aspirin (75-100 mg with US 81 mg/day) has been widely administered for ASCVD prevention. By irreversibly inhibiting platelet function, aspirin reduces risk of atherothrombosis but at the risk of bleeding, particularly in the gastrointestinal (GI) tract. Aspirin is well established for secondary prevention of ASCVD and is widely recommended for this indication, but recent studies have shown that in the modern era, aspirin should not be used in the routine primary prevention of ASCVD due to lack of net benefit. Most important is to avoid aspirin in persons with increased risk of bleeding including a history of GI bleeding or peptic ulcer disease, bleeding from other sites, age >70 years, thrombocytopenia, coagulopathy, chronic kidney disease, and concurrent use of nonsteroidal anti-inflammatory drugs, steroids, and anticoagulants. The following are recommendations based on meta-analysis and three recent trials:

- Low-dose aspirin might be considered for primary prevention of ASCVD in select higher ASCVD adults aged 40-70 years who are not at increased bleeding risk.
- Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults >70 years.
- Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk.

Prophylaxis

Patients at risk for atherosclerosis-related diseases are increasingly being treated prophylactically with low-dose aspirin and a statin. The high incidence of cardiovascular disease led Wald and Law to propose a Polypill, a once-daily pill containing these

two types of drugs in addition to an ACE inhibitor, diuretic, beta blocker, and folic acid. They maintain that high uptake by the general population by such a Polypill would reduce cardiovascular mortality by 80%. It must be emphasized however that this is purely theoretical, as the Polypill has never been tested in a clinical trial.
Medical treatments often focus predominantly on the symptoms. However, over time, the treatments which focus on decreasing the underlying atherosclerosis processes, as opposed to simply treating the symptoms resulting from the atherosclerosis, have been shown by clinical trials to be more effective.

General material and educational and methodological support of the lecture:
- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for the self-control
1. Give definition of Atherosclerosis
2. What is the risk factor of atherosclerosis
3. What factors lead to atherosclerosis
4. Classification of atherosclerosis
5. Stages of pathophysiology
6. Clinical manifestations of atherosclerosis
7. Laboratory and instrumental diagnostics of Atherosclerosis
8. Principles and methods of Atherosclerosis treatment.
9. Prophylaxis of atherosclerosis

List of used sources:

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2. https://cprguidelines.eu/
3. Harrison's Endocrinology. Ed. by J. Larry Jameson, Mc Graw – Hill., New York, Chicago,Toronto. e.a. 5rd edition, 2019. - 608 p.
4. Clinical Medicine. Adam Feather MBBS, FRCP, FAcadMEd. David Randall MA, MRCP. Mona Waterhouse MA (Oxon), MRCP. London New York Oxford Philadelphia St Louis Sydney 2021

Lecture № 3

Topic: Chronic forms of ischemic heart disease

Actuality of theme: Coronary artery disease (also called coronary heart disease or ischemic heart disease) is the number-one killer of both men and women in the United States, and it's the most common type of heart disease. This often preventable disease causes the dangerous thickening and narrowing of the coronary arteries—the vessels that bring blood to the heart—which disrupts the flow of oxygen and nutrients to the heart, causing serious problems.

Goal: explain the essence of the chronic Ischemic heart disease, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: chronic Ischemic heart disease, stable angina, vasospastic angina, chest pain, ECG, nitrates, b-blockers

Lecture plan and organizational structure

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease i. Treatment j. Prevention	 II II II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Ischemic or ischemic heart disease (IHD), or myocardial ischemia, is a disease characterized by ischemia (reduced blood supply) to the heart muscle, usually due to coronary artery disease (atherosclerosis of the coronary arteries). Its risk increases with age, smoking, hypercholesterolemia (high cholesterol levels), diabetes, and hypertension (high blood pressure), and is more common in men and those who have close relatives with ischemic heart disease.

Symptoms of stable ischemic heart disease include angina (characteristic chest pain on exertion) and decreased exercise tolerance. Unstable IHD presents itself as chest pain or other symptoms at rest, or rapidly worsening angina. Diagnosis of IHD is with an electrocardiogram, blood tests (cardiac markers), cardiac stress testing or a coronary angiogram. Depending on the symptoms and risk, treatment may be with medication, percutaneous coronary intervention (angioplasty) or coronary artery bypass surgery (CABG).

It is the most common cause of death in most Western countries, and a major cause of hospital admissions. There is limited evidence for population screening, but prevention (with a healthy diet and sometimes medication for diabetes, cholesterol and high blood pressure) is used both to prevent IHD and to decrease the risk of complications.

The medical history distinguishes between various alternative causes for chest pain (such as dyspepsia, musculoskeletal pain, pulmonary embolism). As part of an assessment of the three main presentations of IHD, risk factors are addressed. These are the main causes of atherosclerosis (the disease process underlying IHD): age, male sex, hyperlipidemia (high cholesterol and high fats in the blood), smoking, hypertension (high blood pressure), diabetes, and the family history.

Assessment of event risk

Assessment of event risk is recommended in every patient being evaluated for suspected CAD or with a newly diagnosed CAD, as it has major impacts on therapy decisions. The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms. Event risk stratification is usually based on the assessments used to make a diagnosis of CAD. All patients should undergo cardiovascular event risk stratification using clinical evaluation, the assessment of LV function by resting echocardiography, and, in the majority of cases, non-invasive assessment of ischemia or coronary anatomy. Although the diagnostic value of an exercise ECG is limited, the occurrence of ST segment depression at a low workload combined with exertional symptoms (angina or dyspnea), low exercise capacity, complex ventricular ectopy, or arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality. Patients with typical angina and LV

systolic dysfunction in a pattern that indicates CAD are also at high risk of cardiac mortality. ICA for risk stratification will only be required in a selected subgroup of patients and additional FFR may be required for event risk stratification as appropriate .

Signs and symptoms

- suspected coronary artery disease with symptoms of 'stable' angina and/or dyspnea
- suspected coronary artery disease and new-onset heart failure or left ventricular dysfunction
- symptomatic or asymptomatic individuals with stabilized symptoms <1 year after an acute coronary syndrome or recent revascularization
- symptomatic or asymptomatic individuals >1 year after the initial diagnosis of coronary artery disease or coronary revascularization
- asymptomatic individuals in whom coronary artery disease was detected at screening
- symptoms of angina in suspected vasospastic coronary disease or microvascular disease

An exercise electrocardiogram can assess exercise tolerance and offers complementary information. ST-segment depression at low workload with associated symptoms as angina or dyspnea, arrhythmias and abnormal blood pressure indicates high risk .

Angina pectoris

Angina pectoris, commonly known as angina, is severe chest pain due to ischemia (a lack of blood and hence oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries(the heart's blood vessels). Coronary artery disease, the main cause of angina, is due to atherosclerosis of the cardiac arteries. The term derives from the Latin angina ("infection of the throat") from the Greekἀγχόνηankhone ("strangling"), and the Latin pectus ("chest"), and can therefore be translated as "a strangling feeling in the chest".

There is a weak relationship between severity of pain and degree of oxygen deprivation in the heart muscle (i.e., there can be severe pain with little or no risk of a heart attack, and a heart attack can occur without pain).

Worsening ("crescendo") angina attacks, sudden-onset angina at rest, and angina lasting more than 15 minutes are symptoms of unstable angina (usually grouped with similar conditions as the acute coronary syndrome). As these may herald myocardial infarction (a heart attack), they require urgent medical attention and are generally treated as a presumed heart attack.

Stable angina

Also known as effort angina, this refers to the more common understanding of angina related to myocardial ischemia. Typical presentations of stable angina is that of chest discomfort and associated symptoms precipitated by some activity (running, walking, etc.) with minimal or non-existent symptoms at rest. Symptoms typically abate several minutes following cessation of precipitating activities and resume when activity resumes. In this way, stable angina may be thought of as being similar to claudication symptoms.

Microvascular angina

Microvascular Angina or Angina Syndrome X is characterized by angina-like

chest pain, but have different causes.The cause of Microvascular Angina is unknown, but it appears to be the result of poor function in the tiny blood vessels of the heart, arms and legs. Since microvascular angina isn't characterized by arterial blockages, it's harder to recognize and diagnose, but its prognosis is excellent.

Signs and symptoms

Most patients with angina complain of chest discomfort rather than actual pain: the discomfort is usually described as a pressure, heaviness, tightness, squeezing, burning, or choking sensation. Apart from chest discomfort, anginal pains may also be experienced in the epigastrium (upper central abdomen), back, neck area, jaw, or shoulders. This is explained by the concept of referred pain, and is due to the spinal level that receives visceral sensation from the heart simultaneously receiving cutaneous sensation from parts of the skin specified by that spinal nerve's dermatome, without an ability to discriminate the two. Typical locations for referred pain are arms (often inner left arm), shoulders, and neck into the jaw. Angina is typically precipitated by exertion or emotional stress. It is exacerbated by having a full stomach and by cold temperatures. Pain may be accompanied by breathlessness, sweating and nausea in some cases. In this case, the pulse rate and the blood pressure increases. The pain usually lasts for about 3 to 5 minutes but the symptoms actually starts 15 to 20 minutes before the cardiac arrest and the pain is relieved by rest or specific anti-angina medication. Chest pain lasting only a few seconds is normally not angina.

Myocardial ischemia comes about when the myocardia (the heart muscles) receive insufficient blood and oxygen to function normally either because of increased oxygen demand by the myocardia or by decreased supply to the myocardia. This inadequate perfusion of blood and the resulting reduced delivery of oxygen and nutrients is directly correlated to blocked or narrowed blood vessels.

Some experience "autonomic symptoms" (related to increased activity of the autonomic nervous system) such as nausea, vomiting and pallor.

Major risk factors for angina include cigarette smoking, diabetes, high cholesterol, high blood pressure, sedentary lifestyle and family history of premature heart disease.

A variant form of angina (Prinzmetal's angina) occurs in patients with normal coronary arteries or insignificant atherosclerosis. It is thought to be caused by spasms of the artery. It occurs more in younger women.

Cause

Major risk factors

- Age (≥ 55 yo for men, ≥ 65 for women)
- Cigarette smoking
- Diabetes mellitus (DM)
- Dyslipidemia
- Family History of premature CVD (men <55 yo, female <65)
- Hypertension (HTN)
- Kidney disease (microalbuminuria or GFR<60 mL/min)
- Obesity (BMI ≥ 30 kg/m2)
- Physical inactivity

Conditions that exacerbate or provoke angina

- Medications
- vasodilators
- excessive thyroid replacement
- vasoconstrictors

Smoking

One study found that smokers with coronary artery disease had a significantly increased level of sympathetic nerve activity when compared to those without. This is in addition to increases in blood pressure, heart rate and peripheral vascular resistance associated with nicotine which may lead to recurrent angina attacks. Additionally, CDC reports that the risk of CHD, stroke, and PVD is reduced within 1–2 years of smoking cessation. In another study, it was found that after one year, the prevalence of angina in smoking men under 60 after an initial attack was 40% less in those who had quit smoking compared to those who continued. Studies have found that there are short term and long term benefits to smoking cessation.

Other medical problems

- profound anemia
- uncontrolled HTN
- hyperthyroidism
- hypoxemia

Other cardiac problems

- tachyarrhythmia
- bradyarrhythmia
- valvular heart disease
- hypertrophic cardiomyopathy

Myocardial ischemia can result from:

- a reduction of blood flow to the heart that can be caused by stenosis, spasm, or acute occlusion (by an embolus) of the heart's arteries.
- resistance of the blood vessels. This can be caused by narrowing of the blood vessels; a decrease in radius. Blood flow is inversely proportional to the radius of the artery to the fourth power.
- reduced oxygen-carrying capacity of the blood, due to several factors such as a decrease in oxygen tension and hemoglobin concentration. This decreases the ability to of hemoglobin to carry oxygen to myocardial tissue.

Atherosclerosis is the most common cause of stenosis (narrowing of the blood vessels) of the heart's arteries and, hence, angina pectoris. Some people with chest pain have normal or minimal narrowing of heart arteries; in these patients, vasospasm is a more likely cause for the pain, sometimes in the context of Prinzmetal's angina and syndrome X.

Myocardial ischemia also can be the result of factors affecting blood composition, such as reduced oxygen-carrying capacity of blood, as seen with severe anemia (low number of red blood cells), or long-term smoking.

Pathophysiology

Angina results when there is an imbalance between the heart's oxygen demand and supply. This imbalance can result from an increase in demand (e.g. during exer-

cise) without a proportional increase in supply (e.g. due to obstruction or atherosclerosis of the coronary arteries).

Diagnosis

Suspect angina in people presenting with tight, dull, or heavy chest discomfort which is:

1. Retrosternal or left-sided, radiating to the left arm, neck, jaw, or back.
2. Associated with exertion or emotional stress and relieved within several minutes by rest.
3. Precipitated by cold weather or a meal.

Some people present with atypical symptoms, including breathlessness, nausea, or epigastric discomfort or burping. These atypical symptoms are particularly likely in older people, women, and those with diabetes.

Angina pain is not usually sharp or stabbing or influenced by respiration. Antacids and simple analgesia do not usually relieve the pain. If chest discomfort (of whatever site) is precipitated by exertion, relieved by rest, and relieved by glyceryl trinitrate, the likelihood of angina is increased.

In angina patients who are momentarily not feeling any one chest pain, an electrocardiogram (ECG) is typically normal, unless there have been other cardiac problems in the past. During periods of pain, depression or elevation of the ST segment may be observed. To elicit these changes, an exercise ECG test ("treadmill test") may be performed, during which the patient exercises to their maximum ability before fatigue, breathlessness or, importantly, pain intervenes; if characteristic ECG changes are documented (typically more than 1 mm of flat or down sloping ST depression), the test is considered diagnostic for angina. Even constant monitoring of the blood pressure and the pulse rate can lead us to some conclusion regarding the angina. The exercise test is also useful in looking for other markers of myocardial ischemia: blood pressure response (or lack thereof, particularly a drop in systolic pressure), dysrhythmia and chronotropic response. Other alternatives to a standard exercise test include a thallium scintigram (in patients who cannot exercise enough for the purposes of the treadmill tests, e.g., due to asthma or arthritis or in whom the ECG is too abnormal at rest) or Stress

The following sections describe some features of different diagnostic tests.

It should be noted that the performance of a given test in different studies varies due to numerous reasons, such as population selection and referral bias. Another potentially important source of variation or bias is the inclusion of a patient in a study based on previous test results or known coronary artery disease (CAD), such as a stenosis on coronary computed tomography angiography (CTA).

Therefore, differences between techniques and summary estimates based on meta-analyses should be interpreted with caution, and considered as directional only.

Exercise electrocardiogram testing

Exercise electrocardiogram (ECG) testing aims to indirectly detect myocardial ischemia through exercise-induced ST-T-segment changes. The main diagnostic ECG abnormality consists of horizontal or down-sloping ST-segment depression >_0.1 mV, persisting for >_0.060.08 s after the J-point, in one or more ECG leads.

Exercise ECG is of no diagnostic value in the presence of left bundle branch

block (LBBB), paced rhythm, and Wolff Parkinson White syndrome, in which cases the ST-T-segment changes are not interpretable. Additionally, false-positive results are more frequent in patients with abnormal resting ECG in the presence of left ventricular (LV) hypertrophy, electrolyte imbalance, intraventricular conduction abnormalities, atrial fibrillation, or who are being treated with digitalis. To obtain diagnostic information, the test should be symptom/ sign-limited and performed without the influence of anti-ischemic drugs. There are numerous reviews and meta-analyses regarding the performance of exercise ECG for the diagnosis of CAD, which have shown variable diagnostic yields. In a recent meta-analysis, the sensitivity and specificity for the detection of CAD, defined as diameter stenosis >_50%, was 58 and 62%, respectively.1 Studies designed to avoid workup bias have reported lower sensitivities (4550%) and higher specificities (8590%).The addition of cardiopulmonary exercise testing may improve sensitivity, but this combination of tests is not widely used.

The diagnostic performance of exercise ECG is inferior to imaging diagnostic tests and inconclusive results are not infrequent, for example, when 85% of maximum heart rate is not achieved in the absence of symptoms or signs of ischemia, when exercise is limited by orthopedic or other non-cardiac problems, or when ECG changes are equivocal. As a result, additional downstream testing is needed more frequently after exercise ECG than after diagnostic tests using imaging. However, depending on the availability of other tests, exercise ECG may be considered as an alternative diagnostic test to detect obstructive CAD. Exercise testing on either a bicycle ergometer or a treadmill provides information other than ST-segment changes on event risk, as well as exercise tolerance, symptoms, heart rate response, arrhythmias, and blood pressure (BP) response Therefore, exercise ECG remains a useful test in many patients with suspected CAD and is widely available. Exercise stress testing can also be useful to evaluate the efficacy of medical treatment or after revascularization, or to aid the prescription of exercise after control of symptoms. For these indications, exercise stress testing should be performed in patients receiving treatment to evaluate control of ischemia or effort performance. The effect of routine periodic exercise testing on patient outcomes has not been formally evaluated.

Echocardiography.

In patients in whom such noninvasive testing is diagnostic, a coronary angiogram is typically performed to identify the nature of the coronary lesion, and whether this would be a candidate for angioplasty, coronary artery bypass graft (CABG), treatment only with medication, or other treatments. There has been researches which concludes that a frequency is attained when there is increase in the blood pressure and the pulse rate. This frequency varies normally but the range is 45-50 khz for the cardiac arrest or for the heart failure. In patients who are in hospital with unstable angina (or the newer term of "high risk acute coronary syndromes"), those with resting ischemic ECG changes or those with raised cardiac enzymes such as troponin may undergo coronary angiography directly.

Single-photon emission computed tomography

Single-photon emission computed tomography (SPECT) myocardial perfusion

imaging produces images of regional myocardial tracer uptake, which reflect relative myocardial blood flow at rest, and during dynamic exercise or pharmacological stress. Transient ischemic dilatation and reduced post-stress ejection fraction are important non-perfusion predictors of severe CAD. The technique provides information on the presence or absence, as well as the location and extent, of myocardial ischemia, myocardial infarction (MI) (and viability), and ventricular function. The SPECT studies can be performed either using an exercise test or using pharmacological stress testing, especially in patients who are unable to exercise adequately or present with LBBB. With the most commonly used technetium-99m radiopharmaceuticals, the estimated radiation exposure to the patient is 10 mSv, but the radiation dose can be halved with the use of stress-only imaging and new high-efficiency cardiac SPECT cameras. The diagnostic accuracy of exercise and pharmacological stress SPECT myocardial perfusion imaging in the detection of CAD has been studied extensively. A meta-analysis found pooled sensitivity of 87% and specificity of 70% when CAD was defined as angiographic coronary stenosis >50%.1 The test also performs well in studies using a functional definition of CAD based on invasive fractional flow reserve (FFR) (sensitivity 73 - 74% and specificity 79 - 83%).Global reductions in myocardial perfusion, such as in the setting of multivessel disease, may cause underestimation of ischemic burden in the relative perfusion images produced by SPECT. Compared with exercise ECG, SPECT myocardial perfusion imaging is more accurate for the detection of obstructive CAD, and provides additional information on the location of myocardial ischemia and the extent of ischemic burden. The cost-effectiveness of SPECT myocardial perfusion imaging is highest in patients in the higher range of intermediate pretest probability (PTP) of CAD. Positron emission tomography Positron emission tomography (PET) perfusion imaging uses 82Rb, 13N-ammonia, or 15O-water as radioactive myocardial perfusion tracers to evaluate myocardial perfusion and function, at rest and during pharmacological stress. Similar to SPECT, the technique provides information on the presence or absence of myocardial ischemia, location and extent of ischemia, MI, residual viability, and ventricular function. In addition, PET has the unique ability to quantify blood flow in mL/min/g, which allows the detection of microvascular disease and improved evaluation of ischemic burden in multivessel CAD. The risks associated with pharmacological vasodilator stress with regard to SPECT similarly apply to PET. The radiation exposure to the patient is lower than that with SPECT (1 - 4 mSv) due to the short radioactive half-life of PET perfusion tracers. PET myocardial perfusion imaging has high diagnostic performance in the detection of CAD in terms of image quality, interpretative certainty, and diagnostic accuracy.

A meta-analysis of diagnostic studies found pooled sensitivity and specificity of 90 and 85%, respectively, when CAD was defined as angiographic coronary stenosis of >50%, and sensitivity and specificity of 89 and 85%, respectively, when CAD was defined by FFR.1 Image quality of PET is affected less than that of SPECT in obese patients.30 Quantification of myocardial blood flow facilitates the detection of extensive, high-risk CAD (balanced ischemia).3134 Compared with SPECT scanners and radiotracers, PET scanners and perfusion tracers are less widely available, and compared with the other stress imaging techniques, PET is less commonly used to diagnose CAD.

Stress cardiac magnetic resonance

Stress CMR can be performed with pharmacological drugs by assessing both myocardial perfusion and changes in LV wall motion in response to stress. Vasodilator and dobutamine are the main drugs. In clinical practice, physical exercise is never used in stress CMR. Dobutamine will increase flow demand and induce wall motion abnormalities due to ischemia in the presence of CAD, similar to dobutamine stress echocardiography, and the safety profiles are comparable. Vasodilators will increase coronary flow and will cause differences in myocardial perfusion in patients with CAD. The perfusion technique with vasodilator stress perfusion is the most commonly used method. Analyses are either by visual assessment of lowsignal areas with reduced perfusion or with different software tools. There have been several attempts to establish semiquantitative and quantitative CMR perfusion analysis, but the clinical use of these tools remains unclear.37 The diagnostic accuracy of CMR perfusion imaging is high and has several advantages, with no attenuation artefacts, high spatial resolution, and no radiation exposure. In a meta-analysis, pooled sensitivity and specificity for the detection of CAD (defined as diameter stenosis >_50%) was 90 and 80%, respectively. CMR perfusion imaging is also well suited for women,40 but the impact of microvascular disease remains unclear. The main disadvantages are CMR's low availability, the high-level of expertise that is required, nonquantitative analyses, and cost issues.

Hybrid imaging techniques

Hybrid SPECT/CT, PET/CT, and PET/CMR scanners have recently become available. Hybrid imaging enables the combination of coronary anatomy with non-invasive CTA with the detection of myocardial ischemia by perfusion imaging. Since the previous version of the Guidelines, new diagnostic studies on hybrid imaging for evaluation of CAD have been published, and a meta-analysis of available evidence indicates a higher specificity without a significant decrease in sensitivity compared with single techniques. However, there is still a need to clarify which patients can benefit from hybrid imaging and how to optimally combine different modalities. Invasive coronary angiography A number of new hyperaemic and resting indexes for physiological assessment have been introduced recently.

Most recently proposed indexes have been compared with FFR as the standard to test physiological equivalence. Prospective outcome trials are available for FFR and instantaneous wave-free ratio (iwFR).

Treatment

The most specific medicine to treat angina is nitroglycerin. It is a potent vasodilator that makes more oxygen available to the heart muscle. Beta-blockers and calcium channel blockers act to decrease the heart's workload, and thus it's requirement for oxygen. Treatments are balloon angioplasty, in which the balloon is inserted at the end of a catheter and inflated to widen the arterial lumen. Stents to maintain the arterial widening are often used at the same time. Coronary bypass surgery involves bypassing constricted arteries with venous grafts. This is much more invasive that angioplasty.

The main goals of treatment in angina pectoris are relief of symptoms, slowing progression of the disease, and reduction of future events, especially heart attacks and, of course, death. Beta blockers (e.g., carvedilol, propranolol, atenolol) have a large body of evidence in morbidity and mortality benefits (fewer symptoms, less disability

and longer life) and short-acting nitroglycerin medications have been used since 1879 for symptomatic relief of angina

Calcium channel blockers (such as nifedipine (Adalat) and amlodipine), isosorbidemononitrate and nicorandil are vasodilators commonly used in chronic stable angina. A new therapeutic class, called If inhibitor, has recently been made available: ivabradine provides pure heart rate reduction leading to major anti-ischemic and anti-anginal efficacy. ACE inhibitors are also vasodilators with both symptomatic and prognostic benefit and, lastly, statins are the most frequently used lipid/cholesterol modifiers which probably also stabilize existing atheromatous plaque. Low-dose aspirin decreases the risk of heart attack in patients with chronic stable angina, and was previously part of standard treatment, however it has since been discovered that the increase in haemorrhagic stroke and gastrointestinal bleeding offsets this gain so they are no longer advised unless the risk of myocardial infarction is very high.

Exercise is also a very good long term treatment for the angina (but only particular regimens - gentle and sustained exercise rather than intense short bursts), probably working by complex mechanisms such as improving blood pressure and promoting coronary artery collateralisation.

Identifying and treating risk factors for further coronary heart disease is a priority in patients with angina. This means testing for elevated cholesterol and other fats in the blood, diabetes and hypertension (high blood pressure), encouraging stopping smoking and weight optimisation.

The calcium channel blocker nifedipine prolongs cardiovascular event- and procedure-free survival in patients with coronary artery disease. New overt heart failures were reduced by 29% compared to placebo; however, the mortality rate difference between the two groups was statistically insignificant.

Anti-ischaemic drugs

Optimal treatment can be defined as the treatment that satisfactorily controls symptoms and prevents cardiac events associated with CCS, with maximal patient adherence and minimal adverse events.

However, there is no universal definition of an optimal treatment in patients with CCS, and drug therapies must be adapted to each patient's characteristics and preferences.192 Initial drug therapy usually consists of one or two antianginal drugs, as necessary, plus drugs for secondary prevention of CVD. The initial choice of antianginal drug(s) depends on the expected tolerance related to the individual patient's profile and comorbidities, potential drug interactions with coadministered therapies, the patient's preferences after being informed of potential adverse effects, and drug availability. Whether combination therapy with two antianginal drugs [e.g. a beta-blocker and a calcium channel blocker (CCB)] is superior to monotherapy with any class of antianginal drug in reducing clinical events remains unclear.

Beta-adrenergic blockers or CCBs are recommended as the first choice, although no RCT to date has compared this strategy to an alternative strategy using initial prescription of other anti-ischemic drugs, or the combination of a beta-blocker and a CCB.

The results of a network meta-analysis of 46 studies and 71 treatment comparisons supported the initial combination of a beta-blocker and a CCB. The same meta-

analysis suggested that several second-line add-on anti-ischaemic drugs (long-acting nitrates, ranolazine, trimetazidine, and, to a lesser extent, ivabradine) may prove beneficial in combination with a beta-blocker or a CCB as first-line therapy, while no data were available for nicorandil. However, it should be noted that the study pooled RCTs using endpoints of nitrate use, angina frequency, time to angina or to ST-segment depression, and total exercise time, and no study or meta-analysis has yet assessed with sufficient power the influence of combining a beta-blocker or a CCB with a second-line anti-ischemic drug on morbidity or mortality events.198 Regardless of the initial strategy, response to initial antianginal therapy should be reassessed after 24 weeks of treatment initiation.

Available drugs Anti-ischemic drugs have proved benefits regarding symptoms associated with myocardial ischemia but do not prevent cardiovascular events in most patients with CCS.

Nitrates

Short-acting nitrates for acute effort angina Sublingual and spray nitroglycerin formulations provide immediate relief of effort angina. Spray nitroglycerin acts more rapidly than sublingual nitroglycerin. At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope, and lying down enhances venous return and preload) and take nitroglycerin (0.30.6 mg tablet sublingually and not swallowed, or 0.4 mg spray to the tongue and not swallowed or inhaled) every 5 min until the pain disappears, or a maximum of 1.2 mg has been taken within 15 min. During this time frame, if angina persists, immediate medical attention is needed. Nitroglycerin can be administered for prophylaxis before physical activities known to provoke angina. Isosorbidedinitrate (5 mg sublingually) has a slightly slower onset of action than nitroglycerin due to hepatic conversion to mononitrate. The effect of isosorbidedinitrate may last _65 years with a history of CAD without prior MI or HF with reduced ejection fraction undergoing elective PCI, beta-blocker use at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30 day and 3 year followup.

However, in patients with or without previous MI undergoing CABG, beta-blockers were associated with lower risk of long-term mortality and adverse cardiovascular events.219 Other observational studies and meta-analyses have questioned the benefit of long-term (>1 year) beta-blocker therapy in patients with a previous MI.

This is still a matter for debate,225 and uncertainties remain on the comparative role of beta-blockers and angiotensinconverting enzyme (ACE) inhibitors.

Calcium channel blockers. While CCBs improve symptoms and myocardial ischaemia, they have not been shown to reduce major morbidity endpoints or mortality in patients with CCS.

NON-DIHYDROPYRIDINE AGENTS (HEART RATE-LOWERING CALCIUM CHANNEL BLOCKERS)

Verapamil has a large range of approved indications, including all varieties of angina (effort, vasospastic, and unstable), supraventricular tachycardias, and hypertension. Indirect evidence suggests good safety but with risks of heart block, bradycardia, and HF. Compared with metoprolol, the antianginal activity was similar.

Compared with atenonol in hypertension with CAD, verapamil is associated

with fewer cases of diabetes, fewer anginal attacks, and less psychological depression.

Beta-blockade combined with verapamil is not advised (due to risk of heart block).

Diltiazem, with its low-side effect profile, has advantages compared with verapamil in the treatment of effort angina. Like verapamil, it acts by peripheral vasodilation, relief of exercise-induced coronary constriction, a modest negative inotropic effect, and sinus node inhibition. There have been no outcome studies comparing diltiazem and verapamil. In some selected patients, non-DHP agents may be combined with beta-blockers for the treatment of angina. However, on such occasions they must be used under close monitoring of patients' tolerance regarding excessive bradycardia or signs of HF. Use of non-DHP CCBs in patients with LV dysfunction is not advised.

DIHYDROPYRIDINE AGENTS

Long-acting nifedipine. This agent is a powerful arterial vasodilator with few serious side effects. Long-acting nifedipine has been especially well tested in hypertensive anginal patients when added to betablockade. In the large placebo-controlled ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) trial, addition of long-acting nifedipine [60 mg o.d. (once a day)] to conventional treatment of angina had no effect on major cardiovascular event-free survival. Long-acting nifedipine proved to be safe, and reduced the need for coronary angiography and cardiovascular interventions.232 Relative contraindications to nifedipine are few (severe aortic stenosis, hypertrophic obstructive cardiomyopathy, or HF), and careful combination with beta-blockade is usually feasible and desirable. Vasodilatory side effects include headache and ankle oedema. Amlodipine. The very long half-life of amlodipine and its good tolerability make it an effective once-a-day antianginal and antihypertensive agent, setting it apart from drugs that are taken either twice or three times daily. Side effects are few, mainly ankle oedema. In patients with CCS and normal BP (75% receiving a beta-blocker), amlodipine 10 mg/day reduced coronary revascularizations and hospitalizations for angina in a 24 month trial. Exercise-induced ischaemia is more effectively reduced by amlodipine, 5 mg titrated to 10 mg/day, than by the beta-blocker atenolol, 50 mg/day, and their combination is even better. However, the CCBbeta-blocker combination is often underused, even in some studies reporting 'optimally treated' stable effort angina.

Ivabradine has been reported to be non-inferior to atenolol or amlodipine in the treatment of angina and ischaemia in patients with CCS. Adding ivabradine 7.5 mg b.i.d. [bis in die (twice a day)] to atenolol therapy gave better control of heart rate and anginal symptoms. In 10 patients with limiting previous angina enrolled in the morbidity mortality evaluation of the BEAUTIFUL (If Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction) trial, ivabradine did not reduce the composite primary endpoint of cardiovascular death, hospitalization with MI, or HF. Also, in the SIGNIFY (Study Assessing the Morbidity Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease) study, consisting of 19 patients with CAD without clinical HF and a heart rate >_70 b.p.m., there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary composite endpoint of death from cardiovascular causes

or non-fatal MI. Ivabradine was associated with an increase in the incidence of the primary endpoint among 12 049 patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). In 2014, the European Medicines Agency issued recommendations to reduce the risk of bradycardia and placed ivabradine under additional monitoring.240 In aggregate, these results support the use of ivabradine as a second-line drug in patients with CCS. Nicorandil. Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta-blockers. Side effects include nausea, vomiting, and potentially severe oral, intestinal, and mucosal ulcerations.

In the placebo-controlled IONA (Impact Of Nicorandil in Angina) trial (n = 5126), nicorandil significantly reduced the composite of coronary heart disease (CHD) death, non-fatal MI, or unplanned hospital admission for suspected anginal symptoms in patients with CCS, but there was no effect on death from ischaemic heart disease or non ESC.

These results support the use of nicorandil as a secondline drug in patients with CCS.

Ranolazine is a selective inhibitor of the late inward sodium current. Side effects include dizziness, nausea, and constipation. In addition, ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT prolonging drugs. In a placebo-controlled trial of 6560 patients with non-ST-segment elevation ACS, the addition of ranolazine to standard treatment did not prove effective in reducing the primary efficacy endpoint of cardiovascular death, MI, or recurrent ischaemia.

However, in the relatively large subgroup of patients with chronic angina (n = 3565), significant reductions in recurrent ischaemia, worsening angina, and intensification of antianginal therapy were observed. In another placebo-controlled trial of patients with diabetes and CAD receiving one or two antianginal drugs, ranolazine reduced angina and sublingual nitroglycerin use with good tolerability. In the RIVER-PCI (Ranolazine for Incomplete Vessel Revascularization PostPercutaneous Coronary Intervention) trial, ranolazine did not reduce the composite of ischaemia-driven revascularization or hospitalization without revascularization in 2651 patients with a history of chronic angina and incomplete revascularization after PCI, including those with and without PCI for a CAD indication, nor did it reduce angina symptoms at 1 year.

These results support the use of ranolazine as a second-line drug in CCS patients with refractory angina despite commonly used antianginal agents such as beta-blockers, CCBs, and/or long-acting nitrates. Conversely, there is a lack of evidence to support the use of ranolazine in patients with CCS following PCI with incomplete revascularization.

General material and educational and methodological support of the lecture:

- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for the self-control

1. Give definition of IHD
2. What is the risk factor of IHD
3. What factors lead to IHD
4. Classification of IHD
5. Normal findings of ejection fraction by echocardioscopy.
6. Clinical manifestations of IHD
7. Laboratory and instrumental diagnostics of IHD
8. Differential diagnosis of IHD
9. Principles and methods of IHD treatment.
10. Prophylaxis of IHD

List of used sources:

1. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes
2. https://cprguidelines.eu/
3. Harrison's Endocrinology. Ed. by J. Larry Jameson, Mc Graw – Hill., New York, Chicago,Toronto. e.a. 5rd edition, 2019. - 608 p.
4. Clinical Medicine. Adam Feather MBBS, FRCP, FAcadMEd. David Randall MA, MRCP. Mona Waterhouse MA (Oxon), MRCP. London New York Oxford Philadelphia St Louis Sydney 2021

Lecture № 4

Topic: Acute coronary syndrome: unstable angina, acute myocardial infarction

Actuality of theme: Cardiovascular disease is the leading cause of death globally, with nearly half of these deaths due to ischemic heart disease. The proportion of acute coronary syndromes that are ST-segment elevation myocardial infarction (STEMI) is decreasing and the broadening availability of high-sensitivity troponin assays has allowed for so-called rapid rule-out algorithms in patients with suspected non-STEMI (NSTEMI). Although substantial progress has been made in the diagnosis and treatment of acute coronary syndromes, cardiovascular disease remains the leading cause of death worldwide, with nearly half of these deaths due to ischaemic heart disease. Globally, 12% of disability-adjusted life-years lost annually are attributable to ischemic heart disease

Goal: explain the essence of the acute coronary syndrome, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: acute coronary syndrome, myocardial infarction, unstable angina, chest pain, ECG, percutaneus intervention

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease i. Treatment j. Prevention	 II II II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

III	The final stage		References, questions, tasks	10% (10 min)
4.	Lecture summary, general conclusions	III		
5.	Answers to possible questions	III		
6.	Tasks for self-training	III		

Content of the lecture

Acute coronary syndrome

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. In terms of pathology, ACS is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery.

The sub-types of acute coronary syndrome include unstable angina and two forms of myocardial infarction in which heart muscle is damaged. These types are named according to the appearance of the electrocardiogram (ECG/EKG) as non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). There can be some variation as to which forms of MI are classified under acute coronary syndrome.

ACS should be distinguished from stable angina, which develops during exertion and resolves at rest. In contrast with stable angina, unstable angina occurs suddenly, often at rest or with minimal exertion, or at lesser degrees of exertion than the individual's previous angina ("crescendo angina"). New onset angina is also considered unstable angina, since it suggests a new problem in a coronary artery.

Though ACS is usually associated with coronary thrombosis, it can also be associated with cocaine use. Cardiac chest pain can also be precipitated by anemia, bradycardias (excessively slow heart rate) or tachycardias (excessively fast heart rate).

The clinical presentation of acute coronary syndromes (ACS) is broad. It ranges from cardiac arrest, electrical or haemodynamic instability with cardiogenic shock (CS) due to ongoing ischemia or mechanical complications such as severe mitral regurgitation, to patients who are already pain free again at the time of presentation.

The leading symptom initiating the diagnostic and therapeutic cascade in patients with suspected ACS is *acute chest discomfort* described as pain, pressure, tightness, and burning. Chest pain-equivalent symptoms may include dyspnoea, epigastric pain, and pain in the left arm. Based on the electrocardiogram (ECG), two groups of patients should be differentiated:

Patients with acute chest pain and persistent (>20 min) ST-segment elevation. This condition is termed ST-segment elevation ACS and generally reflects an acute total or subtotal coronary occlusion. Most patients will ultimately develop ST-segment elevation myocardial infarction (STEMI). The mainstay of treatment in these patients is immediate reperfusion by primary percutaneous coronary intervention (PCI) or, if not available in a timely manner, by fibrinolytic therapy.

Patients with acute chest discomfort but no persistent ST-segment elevation

[non-ST-segment elevation ACS (NSTE-ACS)] exhibit ECG changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves; or the ECG may be normal.

The pathological correlate at the myocardial level is cardiomyocyte necrosis [non-ST-segment elevation myocardial infarction (NSTEMI)] or, less frequently, myocardial ischemia without cell damage (unstable angina). A small proportion of patients may present with ongoing myocardial ischemia, characterized by one or more of the following: recurrent or ongoing chest pain, marked ST-segment depression on 12-lead ECG, heart failure, and hemodynamic or electrical instability.

Due to the amount of myocardium in jeopardy and the risk of developing CS and/or malignant ventricular arrhythmias, immediate coronary angiography and, if appropriate, revascularization are indicated.

Unstable angina

Unstable angina (UA) (also "crescendo angina;" this is a form of acute coronary syndrome) is defined as angina pectoris that changes or worsens.

It has at least one of these three features:

- it occurs at rest (or with minimal exertion), usually lasting >10 min;
- it is severe and of new onset (i.e., within the prior 4–6 weeks); and/or
- it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously).

UA may occur unpredictably at rest which may be a serious indicator of an impending heart attack. What differentiates stable angina from unstable angina (other than symptoms) is the pathophysiology of the atherosclerosis. The pathophysiology of unstable angina is the reduction coronary flow due to transient platelet aggregation on apparently normal endothelium, coronary artery spasms or coronary thrombosis. The process starts with atherosclerosis, and when inflamed leads to an active plaque, which undergoes thrombosis and results in acute ischemia, which finally results in cell necrosis after calcium entry. Studies show that 64% of all unstable anginas occur between 10 PM and 8 AM when patients are at rest.

In stable angina, the developing atheroma is protected with a fibrous cap. This cap (atherosclerotic plaque) may rupture in unstable angina, allowing blood clots to precipitate and further decrease the lumen of the coronary vessel. This explains why an unstable angina appears to be independent of activity.

Acute myocardial infarction

Acute myocardial infarction (AMI) defines cardiomyocyte necrosis in a clinical setting onsistent with acute myocardial ischaemia. A combination of criteria is required to meet the diagnosis of AMI, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin (hs-cTn) T or I, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

1. Symptoms of myocardial ischaemia.
2. New ischaemic ECG changes.
3. Development of pathological Q waves on ECG.

4. Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.
5. Intracoronary thrombus detected on angiography or autopsy.

2.1.1.1 Type 1 myocardial infarction

Type 1 myocardial infarction (MI) is characterized by atherosclerotic plaque rupture, ulceration, fissure, or erosion with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. The patient may have underlying severe coronary artery disease (CAD) but, on occasion (5–10% of cases), there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women.

2.1.1.2 Type 2 myocardial infarction

Type 2 MI is myocardial necrosis in which a condition other than coronary plaque instability causes an imbalance between myocardial oxygen supply and demand. Mechanisms include hypotension, hypertension, tachyarrhythmias, bradyarrhythmias, anaemia, hypoxaemia, but also by definition, coronary artery spasm, spontaneous coronary artery dissection (SCAD), coronary embolism, and coronary microvascular dysfunction.

2.1.1.3 Types 3–5 myocardial infarction

The universal definition of MI also includes type 3 MI (MI resulting in death when biomarkers are not available) and types 4 and 5 MI [related to PCI and coronary artery bypass grafting (CABG), respectively].

2.1.2 Unstable angina in the era of high-sensitivity cardiac troponin assays

Unstable angina is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. Among unselected patients presenting to the emergency department with suspected NSTE-ACS, the introduction of hs-cTn measurements in place of standard troponin assays resulted in an increase in the detection of MI (∼4% absolute and 20% relative increases) and a reciprocal decrease in the diagnosis of unstable angina. Compared with NSTEMI patients, individuals with unstable angina do not experience acute cardiomyocyte injury/necrosis, have a substantially lower risk of death, and appear to derive less benefit from intensified antiplatelet therapy, as well as an invasive strategy within 72 h. Pathophysiology and epidemiology are discussed in detail elsewhere.

Epidemiology

The long-term epidemiology of coronary heart disease has been studied in multiple longitudinal cohort studies. The 50-year follow-up of the European Seven Countries Study was published in 2020. This study followed 6,500 men who were 40-to-59 years old at the time of enrollment and illustrated changes in the prevalence of risk factors over time, notably demonstrating reductions in smoking and serum cholesterol levels, as well as increases in average blood pressure. As the frequency of risk factors decreased over the study period, the hazard rate for mortality decreased.

Similarly, temporal trends in hospitalizations for acute myocardial infarction (MI) have shown marked reductions over time, with a large cohort from Kaiser Permanente demonstrating a 48% reduction in hospitalizations for ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) between 2000 and 2014. Analysis

of acute MI (AMI) hospitalization trends by race revealed that Caucasian patients had a disproportionate reduction in hospitalizations for AMI compared with Hispanic and Black patients during this period. These findings shed light on persistent racial disparities in cardiovascular disease awareness, treatment, and risk factor optimization. Analysis of the same cohort demonstrated similar disparities when patients were stratified by gender, with the rate of reduction in hospitalization lower among women than men. Despite higher rates of primary prevention, women with AMI are less likely to undergo revascularization and receive treatment for secondary prevention than men. Identification of groups with lagging improvements in outcomes is a key step in achieving equitable healthcare outcomes.

Risk factor

Further risk factor elucidation in 2020 was notable for new insights into the role of malnutrition and smoking in ACS. In a retrospective study in northern Spain, researchers evaluated the nutritional status of patients discharged with a diagnosis of ACS. Using validated tools to determine nutritional status, 8% of patients were found to have moderate-to-severe malnutrition. While the worst nutrition scores were associated with a low body mass index, 8% to 36% of malnourished patients had a body mass index ≥ 25 kg/m^2 depending on the nutritional index used. Poor nutritional status was associated with a two-fold increase in the risk for all-cause death. These findings highlighted the importance of identifying and intervening on this modifiable risk factor.

Smoking tobacco, an important risk factor for ACS, was examined in a large pooled analysis of primary percutaneous coronary intervention (PCI) patients. Increased rates of STEMI among smokers have been well-established. Previous studies have observed a favorable prognosis after STEMI among smokers, with the "smoker's paradox" phenomenon posited to be related to ischemic preconditioning and perhaps reduced infarct size among smokers. Redfors et al. analyzed data from ten randomized controlled trials in which patients underwent primary PCI for STEMI, and infarct size subsequently was characterized by cardiac magnetic resonance imaging or Single Photon Emission Computed Tomography (SPECT). Smokers were, on average, ten years younger than nonsmokers at the time of STEMI and, after adjustment for age and other risk factors, had a higher risk of death or heart failure hospitalization, as well as reinfarction compared with nonsmokers. These findings suggested that the "smoker's paradox" is more likely to be related to the younger age and lower comorbidity burden at the time of STEMI in smokers rather than any protective effect of tobacco use.

Pathophysiology

A myocardial infarction occurs when an atherosclerotic plaque slowly builds up in the inner lining of a coronary artery and then suddenly ruptures, causing catastrophic thrombus formation, totally occluding the artery and preventing blood flow downstream.

Acute myocardial infarction refers to two subtypes of acute coronary syndrome, namely non-ST-elevated myocardial infarction and ST-elevated myocardial infarction, which are most frequently (but not always) a manifestation of coronary artery disease. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade, sometimes resulting in

total occlusion of the artery. Atherosclerosis is the gradual buildup of cholesterol and fibrous tissue in plaques in the wall of arteries (in this case, the coronary arteries), typically over decades. Blood stream column irregularities visible on angiography reflect artery lumen narrowing as a result of decades of advancing atherosclerosis. Plaques can become unstable, rupture, and additionally promote a thrombus (blood clot) that occludes the artery; this can occur in minutes. When a severe enough plaque rupture occurs in the coronary vasculature, it leads to myocardial infarction (necrosis of downstream myocardium).

If impaired blood flow to the heart lasts long enough, it triggers a process called the ischemic cascade; the heart cells in the territory of the occluded coronary artery die (chiefly through necrosis) and do not grow back. A collagen scar forms in its place. Recent studies indicate that another form of cell death called apoptosis also plays a role in the process of tissue damage subsequent to myocardial infarction. As a result, the patient's heart will be permanently damaged. This Myocardial scarring also puts the patient at risk for potentially life threatening arrhythmias, and may result in the formation of a ventricular aneurysm that can rupture with catastrophic consequences.

Injured heart tissue conducts electrical impulses more slowly than normal heart tissue. The difference in conduction velocity between injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be the cause of many lethal arrhythmias. The most serious of these arrhythmias is ventricular fibrillation (V-Fib/VF), an extremely fast and chaotic heart rhythm that is the leading cause of sudden cardiac death. Another life threatening arrhythmia is ventricular tachycardia (V-Tach/VT), which may or may not cause sudden cardiac death. However, ventricular tachycardia usually results in rapid heart rates that prevent the heart from pumping blood effectively. Cardiac output and blood pressure may fall to dangerous levels, which can lead to further coronary ischemia and extension of the infarct.

The cardiac defibrillator is a device that was specifically designed to terminate these potentially fatal arrhythmias. The device works by delivering an electrical shock to the patient in order to depolarize a critical mass of the heart muscle, in effect "rebooting" the heart. This therapy is time dependent, and the odds of successful defibrillation decline rapidly after the onset of cardiopulmonary arrest.

Clinical presentation

Acute chest discomfort in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients may have the following presentations:

- Prolonged (>20 min)
-chest discomfort at rest.
-New-onset (de novo) (<3 month) angina (II or III of the Canadian Cardiovascular Society Classification).
-Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina).
- Post-myocardial infarction (MI) angina.

Typical chest discomfort is characterized by a retrosternal sensation of pain, pressure, or heaviness (‘angina’) radiating to the left arm, both arms, the right arm, the

neck, or the jaw, which may be intermittent (usually lasting several minutes) or persistent.2 Additional symptoms such as sweating, nausea, epigastric pain, dyspnoea, and syncope may be present. Atypical presentations include isolated epigastric pain, indigestion-like symptoms, and isolated dyspnoea or fatigue. Atypical complaints are more often observed in the older patient, in women, and in patients with diabetes, chronic renal disease, or dementia.35 The exacerbation of symptoms by physical exertion, and their relief at rest, increase the probability of myocardial ischaemia. The relief of symptoms after nitrate administration increases the likelihood of NSTE-ACS, but this is not diagnostic as it is also reported in other causes of acute chest pain.5 In patients presenting to the emergency department with suspected MI, overall, the diagnostic performance of chest pain characteristics for MI is limited.5 Older age, male sex, family history of coronary artery disease (CAD), diabetes, hyperlipidaemia, smoking, hypertension, renal dysfunction, previous manifestation of CAD, and peripheral or carotid artery disease increase the likelihood of NSTE-ACS.6,7 Conditions that may exacerbate or precipitate NSTE-ACS include anaemia, infection, inflammation, fever, hypertensive peak, anger, emotional stress, and metabolic or endocrine (particularly thyroid) disorders.

Physical examination

Physical examination is frequently unremarkable in patients with suspected NSTE-ACS. Signs of heart failure or haemodynamic or electrical instability mandate a quick diagnosis and treatment. Cardiac auscultation may reveal a systolic murmur due to ischaemic mitral regurgitation associated with poor prognosis or aortic stenosis [mimicking acute coronary syndromes (ACS)].

Rarely, a systolic murmur may indicate a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect) of a subacute and possibly undetected MI. Physical examination may identify signs of non-coronary causes of chest pain (e.g. pulmonary embolism, acute aortic syndromes, myopericarditis, aortic stenosis) or extracardiac pathologies (e.g. pneumothorax, pneumonia, or musculoskeletal diseases). In this setting, the presence of chest pain that can be reproduced by exerting pressure on the chest wall has a relatively high negative predictive value for NSTE-ACS.

According to the presentation, abdominal disorders (e.g. reflux disease, oesophageal spasm, oesophagitis, gastric ulcer, cholecystitis, or pancreatitis) may also be considered in the differential diagnosis. Differences in blood pressure between the upper and lower limbs or between the arms, irregular pulse, jugular vein distension, heart murmurs, friction rub, and pain reproduced by chest or abdominal palpation are findings suggestive of alternative diagnoses. Pallor, sweating, or tremor may point towards precipitating conditions such as anaemia and thyrotoxicosis.

Electrocardiogram

12-lead electrocardiogram showing ST-segment elevation (orange) in I, aVL and V1-V5 with reciprocal changes (blue) in the inferior leads, indicative of an anterior wall myocardial infarction.

The primary purpose of the electrocardiogram is to detect ischemia or acute coronary injury in broad, symptomatic emergency department populations. However, the standard 12 lead ECG has several limitations. An ECG represents a brief sample in

time. Because unstable ischemic syndromes have rapidly changing supply versus demand characteristics, a single ECG may not accurately represent the entire picture. It is therefore desirable to obtain serial 12 lead ECGs, particularly if the first ECG is obtained during a pain-free episode. Alternatively, many emergency departments and chest pain centers use computers capable of continuous ST segment monitoring. The standard 12 lead ECG also does not directly examine the right ventricle, and is relatively poor at examining the posterior basal and lateral walls of the left ventricle. In particular, acute myocardial infarction in the distribution of the circumflex artery is likely to produce a nondiagnostic ECG. The use of additional ECG leads like right-sided leads V3R and V4R and posterior leads V7, V8, and V9 may improve sensitivity for right ventricular and posterior myocardial infarction. In spite of these limitations, the 12 lead ECG stands at the center of risk stratification for the patient with suspected acute myocardial infarction. Mistakes in interpretation are relatively common, and the failure to identify high risk features has a negative effect on the quality of patient care.

The 12 lead ECG is used to classify patients into one of three groups:

- those with ST segment elevation or new bundle branch block (suspicious for acute injury and a possible candidate for acute reperfusion therapy with thrombolytics or primary PCI),
- those with ST segment depression or T wave inversion (suspicious for ischemia), and
- those with a so-called non-diagnostic or normal ECG.

A normal ECG does not rule out acute myocardial infarction. Sometimes the earliest presentation of acute myocardial infarction is the hyperacute T wave, which is treated the same as ST segment elevation. In practice this is rarely seen, because it only exists for 2–30 minutes after the onset of infarction. Hyperacute T waves need to be distinguished from the peaked T waves associated with hyperkalemia. The current guidelines for the ECG diagnosis of acute myocardial infarction require at least 1 mm (0.1 mV) of ST segment elevation in the limb leads, and at least 2 mm elevation in the precordial leads. These elevations must be present in anatomically contiguous leads. (I, aVL, V5, V6 correspond to the lateral wall; V1-V4 correspond to the anterior wall; II, III, aVF correspond to the inferior wall.) This criterion is problematic, however, as acute myocardial infarction is not the most common cause of ST segment elevation in chest pain patients. Over 90% of healthy men have at least 1 mm (0.1 mV) of ST segment elevation in at least one precordial lead. The clinician must therefore be well versed in recognizing the so-called ECG mimics of acute myocardial infarction, which include left ventricular hypertrophy, left bundle branch block, paced rhythm, early repolarization, pericarditis, hyperkalemia, and ventricular aneurysm.

Cardiac markers

Cardiac markers or cardiac enzymes are proteins that leak out of injured myocardial cells through their damaged cell membranes into the bloodstream. Until the 1980s, the enzymes SGOT and LDH were used to assess cardiac injury. Now, the markers most widely used in detection of MI are MB subtype of the enzyme creatin kinase and cardiac troponins T and I as they are more specific for myocardial injury. The cardiac troponins T and I which are released within 4–6 hours of an attack of MI

and remain elevated for up to 2 weeks, have nearly complete tissue specificity and are now the preferred markers for asssessing myocardial damage. Heart-type fatty acid binding protein is another marker, used in some home test kits. Elevated troponins in the setting of chest pain may accurately predict a high likelihood of a myocardial infarction in the near future. New markers such as glycogen phosphorylase isoenzyme BB are under investigation.

The diagnosis of myocardial infarction requires two out of three components (history, ECG, and enzymes). When damage to the heart occurs, levels of cardiac markers rise over time, which is why blood tests for them are taken over a 24-hour period. Because these enzyme levels are not elevated immediately following a heart attack, patients presenting with chest pain are generally treated with the assumption that a myocardial infarction has occurred and then evaluated for a more precise diagnosis.

Angiography

Angiogram of the coronary arteries.

In difficult cases or in situations where intervention to restore blood flow is appropriate, coronary angiography can be performed. A catheter is inserted into an artery (usually the femoral artery) and pushed to the vessels supplying the heart. A radio-opaque dye is administered through the catheter and a sequence of x-rays (fluoroscopy) is performed. Obstructed or narrowed arteries can be identified, and angioplasty applied as a therapeutic measure. Angioplasty requires extensive skill, especially in emergency settings. It is performed by a physician trained in interventional cardiology.

Histopathology

Microscopy image autopsy specimen of myocardial infarct (7 days post-infarction).

Histopathological examination of the heart may reveal infarction at autopsy. Under the microscope, myocardial infarction presents as a circumscribed area of ischemic, coagulative necrosis (cell death). On gross examination, the infarct is not identifiable within the first 12 hours.

Micrograph of a myocardial infarction with prominent contraction band necrosis.

Although earlier changes can be discerned using electron microscopy, one of the earliest changes under a normal microscope are so-called wavy fibers. Subsequently, the myocyte cytoplasm becomes more eosinophilic (pink) and the cells lose their transversal striations, with typical changes and eventually loss of the cell nucleus. The interstitium at the margin of the infarcted area is initially infiltrated with neutrophils, then with lymphocytes and macrophages, who phagocytose ("eat") the myocyte debris. The necrotic area is surrounded and progressively invaded by granulation tissue, which will replace the infarct with a fibrous (collagenous) scar (which are typical steps in wound healing). The interstitial space (the space between cells outside of blood vessels) may be infiltrated with red blood cells.

These features can be recognized in cases where the perfusion was not restored; reperfused infarcts can have other hallmarks, such as contraction band necrosis.

Management

Despite advances in the management of acute MI, patients presenting with MI

and out-of-hospital cardiac arrest continue to have high rates of mortality. Several key publications in 2020 have further defined the role of immediate angiography in out-of-hospital ventricular fibrillation/ventricular tachycardia (VT/VF) arrest survivors, characterized as patients with MI most likely to present with cardiac arrest, and identified optimal treatment strategies for this group.

Immediate coronary angiography and PCI were recommended by both American and European guideline documents in patients presenting with out-of-hospital cardiac arrest found to have STEMI following the return of spontaneous circulation. In resuscitated cardiac arrest patients with an initial shockable rhythm who do not have a STEMI on an electrocardiogram following resuscitation, coronary angiography historically has been recommended without high-quality evidence supporting this practice. The COACT trial randomized cardiac arrest survivors presenting with an initial rhythm of VT/VF and no STEMI on an electrocardiogram to immediate coronary angiography versus delayed coronary angiography following neurologic recovery.

In 2019, the 90-day results were published, which showed no difference in survival or any secondary endpoints between the immediate angiography and the delayed angiography groups. One-year follow-up of the COACT trial was published in 2020. The findings at one year were consistent with the 90-day outcomes, with no differences in several key endpoints, including survival, MI, revascularization, implantable cardioverter-defibrillator shocks, quality of life, and heart failure hospitalization between the immediate versus delayed angiography groups. This data suggested that it is safe to defer angiography in this group of patients until neurologic recovery without any adverse short- or long-term consequences.

Among patients undergoing urgent PCI for AMI, Kosugi et al identified the characteristics of patients most likely to present with out-of-hospital cardiac arrest. In this study, the authors retrospectively analyzed 480 patients at a single center in Japan who underwent PCI for AMI. Patients who underwent angiography for AMI and presented with out-of-hospital cardiac arrest were compared with patients with AMI not complicated by cardiac arrest. In this selected group of patients, cardiac arrest survivors had a considerably lower in-hospital survival compared with those who presented without cardiac arrest (62% *v* 96%). The authors found that younger age, no use of calcium-channel blockers, worse renal function, higher peak CK-MB, culprit lesion as the left main coronary artery, and presence of a chronic total occlusion were associated with AMI presenting with out-of-hospital cardiac arrest. Smaller infarction size, good renal function, VT/VF as the presenting rhythm, and no need for extracorporeal membrane oxygenation were predictors of in-hospital survival among those presenting with out-of-hospital cardiac arrest.

Optimal postarrest care continued to evolve in 2020. The ideal blood pressure goal in postarrest patients with AMI has been controversial; low blood pressure may result in end-organ hypoperfusion leading to worse neurologic outcomes and larger infarction sizes, while higher blood pressure targets may require higher doses of pressors and lead to more dangerous atrial and ventricular arrhythmias. A patient-level pooled analysis of two randomized controlled trials in postarrest patients with AMI evaluated optimal blood pressure targets. Patients were randomized to a lower or higher target blood pressure (mean arterial pressure [MAP] of 65 mmHg *v* 80-100

mmHg). Despite higher doses of inotropes and pressors, the higher MAP group did not have higher rates of arrhythmias, and the infarction size was smaller. There was no difference in 180-day survival between the two groups. While this analysis failed to demonstrate differences in patient-centered outcomes, the lack of increased arrhythmias at higher doses of pressors provides reassurance that the strategy of higher MAP targets is safe.

Finally, analyses of the SWEDEHEART registry attempted to improve identification of patients at the highest risk of cardiac arrest in the 90 days following hospital discharge for AMI. The authors found that out-of-hospital cardiac arrest was relatively rare in the 120,000 patients included in the analysis, with a <0.3% incidence of subsequent cardiac arrest. In an effort to better identify post-MI patients at the highest risk of out-of-hospital cardiac arrest in the 90 days after discharge, the authors analyzed clinical variables to stratify risk, creating a risk score incorporating six parameters (male sex, diabetes, poor renal function, Killip class II or worse heart failure, new-onset atrial fibrillation and/or flutter, and impaired left ventricular ejection fraction). While this risk score performed better than depressed left ventricular ejection fraction alone, patients in the highest risk group only had a 2% risk of out-of-hospital cardiac arrest. Further research is required to identify the post-MI group at the highest risk of out-of-hospital cardiac arrest which, while rare, is devastating.

Pharmacology

Antiplatelet Agents

Antiplatelet therapy is a pharmacologic cornerstone of the management of ACS. In particular, P2Y12 inhibitors have been the subject of scrutiny as the optimal agent, timing of initiation, and duration of therapy continue to be defined. Several key studies published in 2020 have helped to further elucidate the optimal strategies for the initiation and cessation of P2Y12 inhibitors as well as their roles in special populations.

P2Y12 Inhibitor Initiation

Timely P2Y12 inhibitor initiation in STEMI has been recommended by the United States and European guideline documents. Despite emphasis on early P2Y12 inhibitor administration, data demonstrating improved clinical outcomes with prehospital P2Y12 inhibitor administration is lacking. A hypothesized reason for this lack of benefit is the prolonged time required for gastric transit and absorption. One method that has been explored to address this barrier is crushing P2Y12 inhibitors prior to administration. Vlachojannis et al conducted a randomized trial of more than 700 STEMI patients in the Netherlands investigating the clinical effect of crushed prasugrel.Eligible patients who presented within six hours of symptom onset and were scheduled for primary PCI were randomized to a 60-mg loading dose of prasugrel, administered as crushed or integral tablets. The authors were unable to demonstrate any differences between the two groups with respect to the coprimary endpoints of TIMI 3 flow in the infarct-related artery on initial angiography or the resolution of ST elevation one hour after primary PCI. As the rates of stent thrombosis and mortality in STEMI have decreased dramatically due to improvements in stent engineering, PCI techniques, and STEMI systems of care, it has become increasingly difficult to demonstrate significant outcome differences with new agents or strategies in the setting of STEMI. In this study, the average time from randomization to angiography was just slightly more than

20 minutes. Oral agents, regardless of the administration method, are unlikely to be able to demonstrate a significant difference in such a compressed timeframe.

In order to address the delay in onset of action with current oral agents, the novel P2Y12 inhibitor selatogrel has been developed. This agent is administered subcutaneously and has been shown in pharmacodynamic studies to have a rapid onset of action. In a phase II clinical trial, 47 patients presenting with AMI were randomized to a single dose of selatogrel, 8 or 16 mg, followed by ticagrelor. At 30 minutes, 91% of low-dose and 96% of high-dose patients had effective platelet inhibition that was sustained at 60 minutes. No major side effects or bleeding complications were noted. These initial findings are promising as the agent of choice in the preprocedural management of STEMI continues to be emphasized, and the phase III trial of selatogrel is planned.

The timing of P2Y12 inhibitor initiation in NSTEMI similarly has been a historic area of controversy. The largest study questioning routine pretreatment with P2Y12-inhibitor administration in NSTEACS was the ACCOAST trial, which found that patients pretreated with prasugrel had no benefit in ischemic endpoints and had higher rates of serious bleeding. The DUBIUS study, published in 2020, was an open-label randomized controlled trial of more than 1,400 patients with NSTEMI. Patients were randomized to ticagrelor administration upstream (pretreatment) versus downstream (at the time of angiography). The study was terminated prematurely due to futility at the interim analysis, with no differences in the primary composite efficacy and safety endpoints. These findings, in concert with previously published work, showed that routine P2Y12 pretreatment in NSTEMI is at best not helpful and at worst harmful, with increased bleeding events.

Following the publication of PLATO and TRITON-TIMI 38, the P2Y12 inhibitor of choice in patients with NSTEACS has been prasugrel or ticagrelor. Limited data have supported the choice of one of these agents over the other. Posthoc analysis of the unstable angina and NSTEMI groups of the ISAR-REACT 5 trial compared patients randomized to ticagrelor versus prasugrel. The authors found prasugrel to be superior in reducing the one-year composite endpoint of death, MI, and stroke without increasing the risk of serious bleeding. This posthoc analysis is hypothesis-generating and was limited by the initial open-label trial design; however, the findings are reassuring in that no differences in bleeding were observed when directly comparing prasugrel and ticagrelor in patients with NSTEACS.

Antiplatelet Therapy De-escalation

As the significance of bleeding events has become widely appreciated, P2Y12 inhibitor deescalation and cessation have been an area of considerable interest in ongoing clinical trials. The TWILIGHT trial randomized 9,000 patients who were identified as highrisk for bleeding or ischemic complications to dual-antiplatelet therapy (DAPT) with ticagrelor and aspirin versus ticagrelor monotherapy after successfully completing three months of DAPT. The investigators found a lower risk of serious bleeding in the ticagrelor monotherapy group, with no increase in ischemic outcomes. Several subgroup analyses of the TWILIGHT trial subsequently have been published. In a prespecified subgroup analysis of patients undergoing complex PCI as defined by coronary anatomy and extensive and/or complex stenting techniques, patients in the ticagrelor monotherapy group continued to show benefit compared with those treated

with DAPT despite a theoretically higher risk of stent thrombosis in more complex stenting.

In patients presenting with ACS, a subgroup analysis of patients in the TWILIGHT trial also showed a benefit with ticagrelor monotherapy over DAPT, with the benefit of reduced bleeding events more pronounced among patients with ACS than those with stable ischemic heart disease. Similar results were observed in the TICO study that was designed similarly to TWILIGHT with the exception of limiting enrollment to patients who underwent stenting for ACS. After tolerating DAPT with aspirin and ticagrelor for three months, patients were randomized to ticagrelor monotherapy versus DAPT for the next nine months. Similar to TWILIGHT, the authors found reduced composite bleeding, cardiovascular, and cerebrovascular events in the ticagrelor monotherapy group driven by a reduction in major bleeding (HR 0.56 for major bleeding).

Prasugrel was studied in a similar fashion in the HOST-REDUCE-POLYTECH-ACS trial, which randomized 2,300 patients who underwent stenting for ACS to DAPT with full-dose prasugrel and aspirin versus low-dose prasugrel and aspirin after completing three months of DAPT. Consistent with TWILIGHT and TICO, patients who were treated with low-dose prasugrel and aspirin had lower net adverse clinical events at one year, driven by a reduction in the risk of bleeding. Overall, the available data support early deescalation of P2Y12 inhibitor intensity, particularly among patients at a high risk for bleeding complications.

Special Populations

Special consideration for the P2Y12 inhibitor use in the elderly must take into account unique risk factors in this age group, including increased risk of bleeding, risk of ischemic events, and cotreatment with anticoagulation. Analysis from the SWEDEHEART registry compared patients aged 80 or older who were prescribed DAPT with clopidogrel versus ticagrelor at hospital discharge for a diagnosis of MI. After inverse probability weighting of Cox regression models to adjust for differences in patient and therapy characteristics, the authors found no difference in ischemic outcomes with clopidogrel versus ticagrelor. Ticagrelor use was associated with a significantly higher risk of death and bleeding.

This hypothesis put forth by the registry data was tested in the POPular AGE trial, which randomized 1,000 patients older than 70 presenting with NSTEACS to loading and maintenance doses of clopidogrel versus ticagrelor for one year of treatment. Several key findings are notable from this trial. Premature cessation of ticagrelor was very common, with 47% patients in the ticagrelor group stopping treatment due to bleeding or shortness of breath. Bleeding also was frequent in all subjects but was significantly more common in the ticagrelor group, with 24% of patients experiencing PLATO major or minor bleeding compared with 18% in the clopidogrel group. The composite clinical benefit outcome was noninferior for clopidogrel versus ticagrelor. Overall, this study highlighted the high frequency of bleeding in elderly patients treated with P2Y12 inhibitors and demonstrated reduced bleeding with similar ischemic endpoints with clopidogrel versus more potent P2Y12 inhibitors.

An additional group that merits special consideration are those with known cytochrome p-450 polymorphisms that confer reduced clopidogrel metabolism. Patients

with loss of function mutations of the CYP2C19 gene have reduced concentrations of the active metabolites of clopidogrel, increased platelet reactivity, and an increased risk of subsequent ischemic events. Despite these findings, evidence of improved clinical outcomes when antiplatelet therapy is tailored to individual genetics is lacking The findings of the TAILOR-PCI randomized trial were consistent with the lack of benefit in gene-tailored antiplatelet therapy seen in previous studies. In this trial, 5,300 patients who underwent PCI were randomized to standard therapy with clopidogrel versus genotype-guided therapy with ticagrelor substituted for clopidogrel in patients with CYP2C19 loss of function mutations. There were no differences in composite efficacy or bleeding endpoints in the standard versus genotype-guided therapy groups. These findings underlined previous work that has shown that while genotyping can identify higher risk individuals, no effective interventions have been identified to ameliorate this risk.

Lipid-Lowering Agents

The role of lipids in atherogenesis is foundational in the pathogenesis of coronary artery disease. Identifying and targeting lipid metabolites have further elucidated the mechanistic role of lipid-lowering therapies. The importance of very-low-density lipoproteins (VLDL) was demonstrated in analysis from the Copenhagen General Population Study. This observational study found that elevated VLDL cholesterol explained half of the MI risk from elevated apoB-containing lipoproteins, whereas VLDL triglycerides did not account for risk. This was theorized to be due to an increased direct uptake of VLDL into macrophages, which then morphologically become foam cells, a key component of atherosclerotic lesions. These findings guided future directions for study to reduce MI risk by identifying novel lipid targets.

The most recent major advance in anti-lipid therapy has been the development and approval of evolocumab and alirocumab, monoclonal PCSK-9 inhibitors. In the landmark FOURIER and ODYSSEY trials, these agents were shown to significantly reduce low density lipoprotein (LDL) levels and adverse cardiovascular outcomes. A prespecified analysis from the ODYSSEY trial evaluated the effect of alirocumab-induced changes in lipoprotein A (Lp(a)) and LDL-C on major adverse cardiovascular events. The authors found that both baseline levels and relative reductions of Lp(a) and LDL-C were associated independently with a reduction in major adverse cardiovascular events. While providing mechanistic insight into the effect of alirocumab, these findings suggested that Lp(a) may have additional value as an independent treatment target after ACS.

The role of plaque burden and composition in ACS has continued to guide future directions for research. In a large CTA dataset, investigators found that after stratifying patients by calcified plaque burden, the degree of stenosis did not predict future cardiovascular events. That is to say, patients with a similar amount of plaque had a similar risk for subsequent MI whether the plaque was diffuse; eg, non-obstructive versus focal; eg, obstructive. These findings suggested that plaque burden rather than the degree of stenosis may predict future risk.

Intracoronary imaging has furthered the study of plaque burden and characteristics in vivo. Using near-infrared spectroscopy intravascular imaging, investigators in an international prospective cohort study imaged nonculprit segments in 1,500 patients

undergoing cardiac catheterization for suspected coronary artery disease. Investigators were able to demonstrate the association of large lipid-rich plaques with major cardiac events over the next two years at both a patient and plaque level.

The concept that high-risk plaques can be identified and prophylactically treated before progressing to ACS was explored in the PROSPECT ABSORB study. In this pilot trial, patients who underwent successful PCI for STEMI or NSTEACS underwent three-vessel intravascular imaging with intravascular ultrasound and near-infrared spectroscopy. Of the 902 patients enrolled, 182 had lesions eligible for randomization. Lesions that were <70% stenosed with ≥65% plaque burden were randomized to treatment with Absorb bioresorbable vascular scaffold and guideline-directed medical therapy versus medical therapy alone. The investigators found that PCI of angiographically mild lesions with large plaque burdens was safe and associated with a larger minimal lumen area on follow-up angiography. There were similar rates of target lesion failure at 24 months. While underpowered to detect any differences in long-term clinical outcomes, this trial provided reassuring safety data in preparation for a larger pivotal trial. Further study and refinement of identification of the highest risk plaques, as well as robust outcome and safety data, are required before the adoption of PCI with bioresorbable vascular scaffold is adopted.

Miscellaneous Medications

Intravenous (IV) morphine historically has been recommended to control pain in patients with ACS despite the absence of safety data. Given the negative effects of opioids on gastrointestinal motility, IV morphine prior to PCI in the setting of ACS has been theorized to delay the absorption of P2Y12 inhibitors that rely on gastric motility for transit to the intestine where absorption occurs. Delayed absorption with lower circulating concentrations of P2Y12 inhibitors and their metabolites in the time period immediately surrounding PCI has been theorized to increase thrombotic events and lead to higher mortality in patients receiving IV morphine prior to PCI. Previous data in this area have been conflicting, with some studies showing an impact on all-cause mortality and composite endpoints and other studies failing to show any difference in outcomes in those receiving IV morphine versus those who do not.

A posthoc analysis from the EARLY ACS trial examined a group of patients pretreated with clopidogrel prior to coronary angiography for NSTEACS and compared the group who received IV morphine to those who did not. After propensity matching, the group treated with morphine had a higher rate of the composite endpoints of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours (odds ratio 1.40). Periprocedural MI also was increased significantly in the morphine group, suggesting that stent thrombosis and thrombotic complications may be driving these findings. These findings demonstrated the evolving role of opioids in patients with ACS, particularly among patients pretreated with clopidogrel, as pharmacologic studies have shown both delay in absorption, as well as reduced levels of clopidogrel and its metabolites when coadministered with IV morphine. In patients receiving clopidogrel and IV opioids prior to PCI, intensive antiplatelet therapy with IV cangrelor, an IV GP IIB/IIIA inhibitor, or a reloading dose in six hours can be considered to reduce the risk of acute thrombotic events.

Following MI, the use of nonsteroidal antiinflammatory drug (NSAID) medications has been shown to be associated with increased rates of cardiovascular events and bleeding. Despite recommendations to avoid NSAIDs in patients with a history of ischemic heart disease, rates of exposures to NSAIDs remain high due to the presence of other comorbidities. In a nationwide cohort study from Korea with data from more than 100,000 patients who were diagnosed with their first MI, NSAID use was associated significantly with cardiovascular events (HR 9.96) and bleeding events (HR 4.08). Among the NSAIDs prescribed, celecoxib and meloxicam had the lowest adjusted rates of cardiovascular events and bleeding, suggesting that these agents may be the NSAIDs of choice in patients with a history of MI in whom NSAIDs cannot be avoided.

Inflammation has been known to play an important role in the pathophysiology of ACS. After the pivotal CANTOS trial, which demonstrated improved cardiovascular outcomes after treatment with an anti-inflammatory agent, interest has grown in the use of other immunomodulating agents in patients with coronary artery disease. Multiple key publications in 2020 investigated colchicine for secondary prevention in this group. The LoDoCo2 trial randomized patients with angiographic or computed tomography evidence of coronary disease to colchicine versus placebo. In this group of stable patients who had no clinical events in the six months leading to enrollment, colchicine was associated with a reduction in the composite endpoints of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven revascularization (HR 0.69).

These results were concordant with the previously published COLCOT trial, which randomized nearly 5,000 patients with recent MI to colchicine versus placebo. In COLCOT, treatment with low-dose colchicine was associated similarly with lower composite risks of cardiovascular death, cardiac arrest, MI, stroke, or urgent coronary revascularization at two years. A subsequent analysis of time to treatment with colchicine in the COLCOT trial demonstrated that the benefit of colchicine was greatest in those who started treatment with colchicine within three days of MI (HR of 0.52) compared with those who started treatment more than eight days after revascularization (HR 0.82)

These positive findings were tempered with contradictory data from a smaller multicenter randomized controlled trial from Australia (the Australian COPS trial). In a design similar to COLCOT, investigators randomized patients who presented with ACS with angiography showing coronary artery disease to one year of colchicine versus placebo prior to hospital discharge. No difference was found with respect to the primary composite endpoint and, concerningly, a higher rate of noncardiovascular mortality was observed in the colchicine group. Several important limitations are notable, including the premature cessation of the trial prior to enrolling the target number of subjects due to slow enrollment, as well as a significant number of patients lost to follow-up. Despite concerns regarding statistical power and generalizability of this study, the findings limited enthusiasm for the wide uptake of colchicine in the post-MI population as further safety data are awaited.

Some exploratory studies have examined the role of colchicine at the time of PCI. The COLCHICINE-PCI randomized trial was a single-site trial, which randomized patients undergoing PCI to a one-time oral dose of colchicine versus placebo at

the time of PCI. Patients were followed for 30-day composite endpoints of death, MI, and target-vessel revascularization, periprocedural MI, and inflammatory biomarkers. Despite attenuation in IL-6 and hs-CRP concentrations at 24 hours after PCI, no differences were seen in clinical endpoints. Pre- and periprocedural use of colchicine remains an ongoing question which is a subject of ongoing research.

Prevention

The risk of a recurrent myocardial infarction decreases with strict blood pressure management and lifestyle changes, chiefly smoking cessation, regular exercise, a sensible diet for patients with heart disease, and limitation of alcohol intake.

Patients are usually commenced on several long-term medications post-MI, with the aim of preventing secondary cardiovascular events such as further myocardial infarctions, congestive heart failure or cerebrovascular accident (CVA). Unless contraindicated, such medications may include:

Evidence supports the consumption of polyunsaturated fats instead of saturated fats as a measure of decreasing coronary heart disease.

Antiplatelet drug therapy such as aspirin and/or clopidogrel should be continued to reduce the risk of plaque rupture and recurrent myocardial infarction. Aspirin is first-line, owing to its low cost and comparable efficacy, with clopidogrel reserved for patients intolerant of aspirin. The combination of clopidogrel and aspirin may further reduce risk of cardiovascular events, however the risk of hemorrhage is increased.

Beta blocker therapy such as metoprolol or carvedilol should be commenced. These have been particularly beneficial in high-risk patients such as those with left ventricular dysfunction and/or continuing cardiac ischemia. β-Blockers decrease mortality and morbidity. They also improve symptoms of cardiac ischemia in NSTEMI.

ACE inhibitor therapy should be commenced 24–48 hours post-MI in hemodynamically-stable patients, particularly in patients with a history of MI, diabetes mellitus, hypertension, anterior location of infarct (as assessed by ECG), and/or evidence of left ventricular dysfunction. ACE inhibitors reduce mortality, the development of heart failure, and decrease ventricular remodelling post-MI.

Statin therapy has been shown to reduce mortality and morbidity post-MI. The effects of statins may be more than their LDL lowering effects. The general consensus is that statins have plaque stabilization and multiple other ("pleiotropic") effects that may prevent myocardial infarction in addition to their effects on blood lipids.

The aldosterone antagonist agent eplerenone has been shown to further reduce risk of cardiovascular death post-MI in patients with heart failure and left ventricular dysfunction, when used in conjunction with standard therapies above. Spironolactone is another option that is sometimes preferable to eplerenone due to cost.

Omega-3 fatty acids, commonly found in fish, have been shown to reduce mortality post-MI. While the mechanism by which these fatty acids decrease mortality is unknown, it has been postulated that the survival benefit is due to electrical stabilization and the prevention of ventricular fibrillation. However, further studies in a high-risk subset have not shown a clear-cut decrease in potentially fatal arrhythmias due to omega-3 fatty acids.

Blood donation may reduce the risk of heart disease for men, but the link has not

been firmly established.

General material and educational and methodological support of the lecture:

- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:

1. Give definition of ACS,Unstable angina, AMI.
2. What is the risk factor of ACS.
3. What factors lead to ACS, AMI.
4. Classification of ACS,AMI.
5. Pathophysiology of AMI.
6. Clinical manifestations of ACS, Unstable angina, AMI.
7. Laboratory and instrumental diagnostics of AMI.
8. Differential diagnosis of AMI.
9. Principles and methods of AMI treatment.
10. Prevention of AMI.

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Lecture № 5

Topic: Pulmonary heart. Pulmonary embolism

Actuality of theme: Pulmonary embolism is an important clinical entity with considerable mortality despite advances in diagnosis and treatment. In the present article, the authors offer a comprehensive review focused mainly on epidemiology, risk factors, risk stratification, pathophysiological considerations and clinical presentation. Diagnosis based on assessment of clinical likelihood, electrocardiography, chest x-ray, D-dimer levels, markers of myocardial injury and overload, and blood gases is discussed in detail. Special attention is devoted to the clinical use of computed tomography, pulmonary angiography and echocardiography in the setting of pulmonary embolism.

Goal: explain the essence of the pulmonary embolism, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention.

Key words: pulmonary embolism, pulmonary heart, chest pain, pulmonary hypertension, CT with angiography, fibrinolysis

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease i. Treatment j. Prevention	 II II II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Pulmonary embolism (PE) is the occlusion of pulmonary arteries by thrombi that originate elsewhere, typically in the large veins of the legs or pelvis. Risk factors for pulmonary embolism are conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulable states.

Etiology of Pulmonary Embolism. Nearly all pulmonary emboli arise from thrombi in the veins of the legs or pelvis (deep venous thrombosis). Risk of embolization is higher with thrombi that reach the popliteal vein or above. Thromboemboli can also originate in arm veins or central veins of the chest (caused by central venous catheters or resulting from thoracic outlet syndromes).

Pulmonary embolism can also arise from nonthrombotic sources (eg, embolism of air, amniotic fluid, fat, infected material, foreign body, tumor).

Risk factors for deep venous thrombosis and pulmonary embolism are similar in children and adults and include

- Conditions that impair venous return, including bed rest and confinement without walking
- Conditions that cause endothelial injury or dysfunction
- Underlying hypercoagulable (thrombophilic) disorders such as cancer or primary clotting disorders

COVID-19 appears to be a risk factor for deep venous thrombosis and pulmonary embolism. Although part of the risk may be due to reduced mobility associated with illness, it is thought that SARS-CoV-2 infection is particularly prothrombotic.

Pathophysiology of Pulmonary Embolism. Once deep venous thrombosis develops, clots may dislodge and travel through the venous system and the right side of the heart to lodge in the pulmonary arteries, where they partially or completely occlude one or more vessels. The consequences depend on the size and number of emboli, the underlying condition of the lungs, how well the right ventricle (RV) is functioning, and the ability of the body's intrinsic thrombolytic system to dissolve the clots. Death occurs due to right ventricular failure.

Small emboli may have no acute physiologic effects and may begin to lyse immediately and resolve within hours or days. Larger emboli can cause a reflex increase in ventilation (tachypnea), hypoxemia due to ventilation/perfusion (V/Q) mismatch and low mixed venous oxygen content as a result of low cardiac output, atelectasis due to alveolar hypocapnia and abnormalities in surfactant, and an increase in pulmonary vascular resistance caused by mechanical obstruction and vasoconstriction resulting in tachycardia and hypotension. Endogenous lysis reduces most emboli, even those

of moderate size, and physiologic alterations decrease over hours or days. Some emboli resist lysis and may organize and persist and sometimes cause chronic pulmonary hypertension.

Pulmonary emboli may be classified according to the physiologic effects as

- High risk (catastrophic or super-massive): Impaired right ventricular function with severe hypotension/hypoxemia that requires aggressive pressor therapy and high-flow oxygen
- High risk (massive): Impaired right ventricular function causing hypotension, as defined by systolic blood pressure < 90 mm Hg or a drop in systolic blood pressure of ≥ 40 mm Hg from baseline for a period of 15 minutes
- Intermediate risk (submassive): Impaired right ventricular function and/or abnormal troponin and/or brain (B-type) natriuretic peptide (BNP) level without hypotension.
- Low risk: Absence of right ventricular impairment and absence of hypotension.

Symptoms and Signs of Pulmonary Embolism. Many pulmonary emboli are small, physiologically insignificant, and asymptomatic. Even when present, symptoms are nonspecific and vary in frequency and intensity, depending on the extent of pulmonary vascular occlusion and preexisting cardiopulmonary function.

Emboli often cause

- Acute dyspnea
- Pleuritic chest pain (when there is pulmonary infarction)

Dyspnea may be minimal at rest and can worsen during activity.

Less common symptoms include

- Cough (usually caused by comorbid disorders)
- Hemoptysis (occasionally occurs when there is pulmonary infarction)

In elderly patients, the first symptom may be altered mental status.

Massive pulmonary emboli may manifest with hypotension, tachycardia, lightheadedness/presyncope, syncope, or cardiac arrest.

The most common signs of pulmonary embolism are tachycardia, tachypnea.

Less commonly, patients have hypotension. A loud 2nd heart sound (S2) due to a loud pulmonic component (P2) is possible but uncommon in acute PE because increases in pulmonary artery pressures are only modest. Crackles or wheezing may occur but is usually due to comorbid disease. In the presence of right ventricular failure, distended internal jugular veins and a RV heave may be evident, and a RV gallop (3rd heart sound [S3]), with or without tricuspid regurgitation, may be audible.

Fever, when present, is usually low-grade unless caused by an underlying condition.

Pulmonary infarction is typically characterized by chest pain (mainly pleuritic) and, occasionally, hemoptysis. The chest wall may be tender.

Chronic thromboembolic pulmonary hypertension causes symptoms and signs of right heart failure, including exertional dyspnea, easy fatigue, and peripheral edema that develops over months to years.

Patients with acute pulmonary embolism may also have symptoms of deep venous thrombosis (ie, pain, swelling, and/or erythema of a leg or an arm). Such leg symptoms are often not present, however.

Diagnosis of Pulmonary Embolism

- High index of suspicion
- Assessment of pretest probability (based on clinical findings, including pulse oximetry and chest x-ray)
- Subsequent testing based on pretest probability

The diagnosis of pulmonary embolism is challenging because symptoms and signs are nonspecific and diagnostic tests are not 100% sensitive and specific. It is important to include PE in the differential diagnosis when nonspecific symptoms, such as dyspnea, pleuritic chest pain, hemoptysis, light-headedness, or syncope are encountered.

Thus, PE should be considered in the differential diagnosis of patients suspected of having cardiac ischemia, heart failure, chronic obstructive pulmonary disease (COPD) exacerbation, pneumothorax, pneumonia, sepsis, acute chest syndrome (in patients with sickle cell disease), acute anxiety with hyperventilation.

Significant, unexplained tachycardia may be a clue. Pulmonary embolism also should be considered in any older patient with tachypnea and altered mental status.

Initial evaluation should include pulse oximetry and chest x-ray. ECG, arterial blood gas (ABG) measurements, or both may help to exclude other diagnoses (eg, acute myocardial infarction).

The **chest x-ray** usually is nonspecific but may show atelectasis, focal infiltrates, an elevated hemidiaphragm, or a pleural effusion. The classic findings of focal loss of vascular markings (Westermark sign), a peripheral, wedge-shaped density arising from the pleura (Hampton hump), or enlargement of the right descending pulmonary artery are suggestive but uncommon (ie, insensitive) and have low specificity. Chest x-ray can also help exclude pneumonia. Pulmonary infarction due to pulmonary embolism may be mistaken for pneumonia.

Pulse oximetry provides a quick way to assess oxygenation; hypoxemia is one sign of PE, and it requires further evaluation. **Blood gas testing** should be considered particularly for patients with dyspnea or tachypnea who do not have hypoxemia detected with pulse oximetry. Arterial or venous blood gas measurement may show an increased alveolar to arterial oxygen (A-a) difference (sometimes called A-a gradient) or hypocapnia. Both of these tests are moderately sensitive for PE, but neither is specific. Blood gas testing should be considered particularly for patients with dyspnea or tachypnea who do not have hypoxemia detected with pulse oximetry. Oxygen saturation may be normal due to a small clot burden, or to compensatory hyperventilation; a very low pCO2 detected with an ABG measurement can confirm hyperventilation.

ECG most often shows tachycardia and various ST-T wave abnormalities, which are not specific for pulmonary embolism. An S1Q3T3 or a new right bundle branch block may indicate the effect of abrupt rise in RV size affecting RV conduction pathways; these findings are moderately specific but insensitive, occurring in only about 5% of patients, although the findings occur in a higher percentage of patients with massive PE. Right axis deviation (R > S in V1) and P-pulmonale may be present. T-wave inversion in leads V1 to V4 also occurs.

Prognosis for Pulmonary Embolism. An estimated 10% of patients with pulmonary embolism die within the first few hours after presentation. Most patients who die as a result of acute PE are never diagnosed before death. In fact, PE is not suspected in most of these patients. The best prospects for reducing mortality involve

- Improving the frequency of diagnosis (eg, by including PE in the differential diagnosis when patients present with nonspecific but compatible symptoms or signs)
- Improving the rapidity of diagnosis
- Improving risk-stratification
- Improving the rapidity of initiation of anticoagulation therapy
- Providing appropriate prophylaxis in at-risk patients

Very high D-dimer levels appear to predict a poor outcome.

General Treatment of Pulmonary Embolism: supportive therapy, anticoagulation, inferior vena cava filter placement (in selected patients), rapid clot burden reduction (in selected patients).

Rapid assessment for the need for supportive therapy should be undertaken. In patients with hypoxemia, oxygen should be given. In patients with hypotension due to massive PE, 0.9% saline can be cautiously given IV; overloading the right ventricle can result in deterioration. Vasopressors may also be given if IV fluids fail to sufficiently increase blood pressure. Norepinephrine is the most commonly used first-line agent. Epinephrine and dobutamine have inotropic effects, but it is not clear how much these affect the normally thin-walled RV.

In general,

- Low-risk patients should receive anticoagulation alone
- High-risk / catastrophic patients require anticoagulation plus additional measures such as systemic thrombolysis or surgical or catheter-directed therapy

Intermediate-risk patients (high or low) are more complicated. Intermediate-low risk patients are most commonly treated with anticoagulation alone. However, the intermediate-risk categories require assessment of their entire clinical picture including: symptoms and signs, severity of RV dysfunction by echocardiography, degree of troponin elevation, amount of oxygen and vasopressor required, clot burden and location.

Anticoagulation is the mainstay of therapy for PE, and rapid reduction of clot burden via thrombolytic therapy or embolectomy is indicated for patients with hypotension that does not resolve after fluid resuscitation, and for *selected* patients with impaired RV function. Placement of a removable percutaneous inferior vena cava filter (IVCF) should be considered for patients with contraindications to anticoagulation or for those with recurrent PE despite anticoagulation. For example, patients who have acute PE and residual clot in the leg and cannot be anticoagulated, should have a filter placed because they have persistent risk of subsequent DVT.

Hospitalization for at least 24 to 48 hours is done for most patients with PE. Patients with abnormal vital signs or massive or submassive PE require longer periods of hospitalization.

Outpatient management may be used for select patients with incidentally discovered PE or those with very small clot burdens and minimal symptoms provided their vital signs are stable, education is undertaken, and a reasonable plan for outpatient treatment and follow-up is in place.

Anticoagulation. Initial anticoagulation followed by maintenance anticoagulation is indicated for patients with acute pulmonary embolism to prevent clot extension and further embolization as well as new clot formation. Anticoagulant therapy for acute PE should be started whenever PE is strongly suspected, as long as the risk of bleeding is deemed low. Otherwise, anticoagulation should be started as soon as the diagnosis is made.

Initial anticoagulation choices for acute PE include

- Intravenous unfractionated heparin
- Subcutaneous low molecular weight heparin
- Subcutaneous fondaparinux
- Factor Xa inhibitors (apixaban and rivaroxaban)
- Intravenous argatroban for patients with heparin-induced thrombocytopenia

Intravenous unfractionated heparin has a short half-life (useful when the potential for bleeding is deemed higher than usual) and is reversible with protamine. An initial bolus of unfractionated heparin is given, followed by an infusion of heparin dosed by protocol to achieve an activated PTT 1.5 to 2.5 times that of normal control. Therefore, unfractionated heparin requires ongoing hospitalization to administer. Further, the pharmacokinetics of unfractionated heparin are relatively unpredictable, resulting in frequent periods of over-anticoagulation and under-anticoagulation and necessitating frequent dose adjustments. Regardless, many clinicians prefer this IV unfractionated heparin regimen, particularly when thrombolytic therapy is given or contemplated or when patients are at risk of bleeding because if bleeding occurs, the short half-life means that anticoagulation is quickly reversed after the infusion is stopped.

Adverse effects of all heparins include: bleeding, thrombocytopenia (including heparin-induced thrombocytopenia with the potential for thromboembolism), urticaria, anaphylaxis (rare).

Bleeding caused by over-heparinization with unfractionated heparin can be treated with a maximum of 50 mg of protamine per 5000 units unfractionated heparin infused over 15 to 30 minutes. Over-heparinization with a low molecular weight heparin can be treated with protamine 1 mg in 20 mL normal saline infused over 10 to 20 minutes, although the precise dose is undefined because protamine only partially neutralizes low molecular weight heparin inactivation of factor Xa.

Fondaparinux is a factor Xa antagonist given subcutaneously. It can be used in acute DVT and acute PE instead of heparin or low molecular weight heparin. It has also been shown to prevent recurrences in patients with superficial venous thrombosis. Outcomes appear to be similar to those of unfractionated heparin. Advantages include once or twice a day fixed-dose administration, no need for monitoring of the degree of anticoagulation, and lower risk of thrombocytopenia. The dose (in mg/kg once a day) is 5 mg for patients < 50 kg, 7.5 mg for patients 50 to 100 kg, and 10 mg for

patients > 100 kg. Fondaparinux dose is decreased by 50% if creatinine clearance is 30 to 50 mL/minute (0.5 to 0.83 mL/second). The drug is contraindicated if creatinine clearance is < 30 mL/minute.

The other **factor Xa inhibitors,** apixaban, rivaroxaban, and edoxaban, have the advantages of oral fixed dosing and the ability to be used as maintenance anticoagulants with no need for laboratory monitoring of the anticoagulant effect. They also cause few adverse interactions with other drugs, although azole antifungal therapy and older HIV therapies (protease inhibitors) will increase oral factor Xa inhibitor drug levels, and certain antiseizure drugs and rifampin will decrease oral factor Xa inhibitor drug levels. Although rivaroxaban and apixaban do not require overlap with a parenteral anticoagulant when used as initial therapy, edoxaban requires use of a parenteral anticoagulant for 5 to 10 days.

Dose reductions are indicated for patients with renal insufficiency. Apixaban can be used in patients with renal insufficiency and data suggest use is safe in patients undergoing hemodialysis.

Anticoagulation reversal of the oral Xa inhibitors (rivaroxaban, apixaban, edoxaban) is possible with andexanet, although this drug is not widely used at this time. Also, the half-lives of the newer factor Xa inhibitors are much shorter than the half-life for warfarin. If bleeding develops that requires reversal, use of 4-factor prothrombin complex concentrate can be considered, and hematology consultation is recommended.

The safety and efficacy of these drugs in patients with pulmonary embolism complicated by severe cardiopulmonary decompensation have not yet been studied, and parenteral drugs should be used for anticoagulation in these patients until there is significant improvement in cardiopulmonary function.

The **direct thrombin inhibitor** dabigatran has also proven effective for treatment of acute DVT and PE. Idarucizumab has proven effective at reversing dabigatran.

Finally, in patients with suspected or proven heparin-induced thrombocytopenia , intravenous argatroban or subcutaneous fondaparinux can be used for anticoagulation. Use of the direct oral anticoagulants is currently being studied in patients with heparin-induced thrombocytopenia, but these drugs appear safe after platelet recovery.

Maintenance anticoagulation is indicated to reduce the risk of clot extension or embolization and to reduce the risk of new clot formation. Drug choices for maintenance anticoagulation include

- Oral vitamin K antagonist (warfarin in the US)
- Oral factor Xa inhibitors (apixaban, rivaroxaban, edoxaban)
- Oral direct thrombin inhibitor (dabigatran)
- Rarely subcutaneous low molecular weight heparin

Warfarin is an effective long-term oral anticoagulant option that has been used for decades, but it is very inconvenient for a number of reasons. In most patients, warfarin is started on the same day as heparin (or fondaparinux) therapy used for initial anticoagulation. Heparin (or fondaparinux) therapy should be overlapped with warfarin therapy for a minimum of 5 days *and* until the INR has been within the therapeutic range (2.0 to 3.0) for at least 24 hours.

The major disadvantages of warfarin are the need for periodic INR monitoring, with frequent dose adjustments, and drug interactions. Physicians prescribing warfarin should be wary of drug interactions; in a patient taking warfarin, virtually any new drug should be checked.
Bleeding is the most common complication of warfarin treatment; patients > 65 years and those with comorbidities (especially diabetes, recent myocardial infarction, hematocrit < 30%, or creatinine > 1.5 mg/dL [>133 micromol/L]) and a history of stroke or gastrointestinal bleeding seem to be at greatest risk. Bleeding can be reversed with vitamin K 2.5 to 10 mg IV or orally and, in an emergency, with fresh frozen plasma or a new concentrate formulation (prothrombin complex concentrates) containing factor II (prothrombin), factor VII, factor IX, factor X, protein C, and protein S. Vitamin K may cause flushing, local pain, and, rarely, anaphylaxis.
Warfarin-induced necrosis, a devastating complication of warfarin therapy, can occur in patients with heparin-induced thrombocytopenia if warfarin is started before platelet recovery. Based on these considerations and the development of more convenient oral anticoagulants, it is likely that warfarin use will decline substantially over the coming years.

The **oral factor Xa inhibitor anticoagulants** apixaban and rivaroxaban can be used for both initial and maintenance anticoagulation therapy. These drugs are more convenient than warfarin due to their fixed dosing and lack of need for laboratory monitoring, as well as having fewer drug interactions. In clinical trials, rivaroxaban, apixaban, and edoxaban were as effective (in non-inferiority analyses) as warfarin in preventing recurrent DVT and PE. A meta-analysis of large phase III randomized controlled trials found that rates of major bleeding, including intracranial hemorrhage, were significantly lower with oral factor Xa inhibitor anticoagulants than with warfarin (5). Another advantage of both rivaroxaban and apixaban is that dosages may be lowered (10 mg orally once a day of rivaroxaban and 2.5 mg orally twice a day of apixaban) after patients have been treated for 6 to 12 months.
Edoxaban requires that a preceding 5 to 10 days of initial heparin or low molecular weight heparin be given.
The direct thrombin inhibitor dabigatran can also be used for maintenance anticoagulation therapy. As with edoxaban, 5 to 10 days of treatment with unfractionated heparin or low molecular weight heparin is needed before dabigatran can be initiated. Clinically relevant bleeding is lower with dabigatran than with warfarin. The use of dabigatran as maintenance therapy has the same advantages and disadvantages as the use of the factor Xa inhibitors.
The need for initial heparin treatment before edoxaban or dabigatran is given is a reflection of the way the clinical trials were conducted.

Aspirin has been studied for long-term maintenance therapy. It appears more effective than placebo but less effective than all other available anticoagulants. Rivaroxaban, 10 mg once/day, has proven more effective at reducing recurrent DVT/PE yet is as safe as aspirin in patients already treated with anticoagulation for 6 to 12 months.

Duration of maintenance anticoagulation for PE is dependent on a variety of factors (eg, risk factors for PE, bleeding risk) and can range from 3 months to lifelong therapy. Clearly transient risk factors (eg, immobilization, recent surgery, trauma) require only 3 months of treatment. Patients with unprovoked PE, those with more durable risk factors for PE (eg, cancer, thrombophilic disorder), and those with recurrent PE might benefit from lifelong anticoagulation provided the bleeding risk is low or moderate. In many patients, degree of risk is less clear (eg, with a minor precipitating factor such as a 4 hour flight); for them, rather than stopping rivaroxaban or apixaban at 6 months, dosage can be decreased.

Risk factors for bleeding include: age > 65 years, previous bleeding, thrombocytopenia, antiplatelet therapy, poor anticoagulant control, frequent falls, liver failure, alcohol abuse, recent surgery, reduced functional capacity, previous stroke, diabetes, anemia, cancer, renal failure.

Low risk for bleeding is defined as no bleeding risk factors, moderate risk for bleeding is defined as one risk factor, and high risk for bleeding is defined as two or more risk factors.

As described above, after 6 months of treatment with rivaroxaban or apixaban, dosage decreases can be considered.

Rapid Reduction of Clot Burden. Clot elimination by means of embolectomy or dissolution with IV or catheter-based thrombolytic therapy should be considered for acute pulmonary embolism associated with hypotension that does not resolve after fluid resuscitation (massive PE). Patients who are hypotensive and require vasopressor therapy are obvious candidates. Patients with a systolic blood pressure < 90 mm Hg lasting at least 15 minutes are hemodynamically compromised and are also candidates.

Although only anticoagulation is generally recommended for patients with very mild RV dysfunction (based on clinical, ECG, or echocardiographic findings), thrombolytic therapy or embolectomy may be needed when RV compromise and/or hypoxemia is severe even when hypotension is not present, particularly when deterioration is likely as suggested by an increase in heart rate or decrease in oxygen saturation or blood pressure.

Catheter-directed PE therapy (thrombolytics, embolectomy) uses catheter placement in the pulmonary arteries for disruption and/or lysis of clot. It is used to treat massive PE. Indications for the treatment of submassive PE are evolving. Studies to date, including prospective randomized clinical trials, have demonstrated that this approach leads to an improved RV/LV ratio at 24 hours compared with anticoagulation alone. Other outcomes and safety of catheter-based therapy compared to systemic thrombolysis are under investigation.

Prevention of Pulmonary Embolism

Prevention of pulmonary embolism means prevention of deep venous thrombosis (DVT); the need depends on the patient's risks, including: type and duration of any surgery, comorbid conditions, including cancer and hypercoagulable disorders, presence of a central venous catheter, prior history of DVT or PE.

Bedbound patients and patients undergoing surgical, especially orthopedic, procedures benefit, and most of these patients can be identified before a thrombus forms. Preventive measures include low-dose unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux, oral anticoagulants (eg, rivaroxaban, apixaban), compression devices, and elastic compression stockings.
Choice of drug or device depends on various factors, including the patient population, the perceived risk, contraindications (eg, bleeding risk), relative costs, and ease of use.

Drug regimens for pulmonary embolism prevention. Drug therapy to prevent DVT is usually begun after surgery to help prevent intraoperative bleeding. However, preoperative prophylaxis is also effective.
In general surgery patients, **low dose unfractionated heparin** is given in doses of 5000 units subcutaneously every 8 to 12 hours for 7 to 10 days or until the patient is fully ambulatory. Immobilized patients not undergoing surgery should receive 5000 units subcutaneously every 8 to 12 hours until they are ambulatory.
Low molecular weight heparin dosing for DVT prophylaxis depends on the specific drug (enoxaparin, dalteparin, tinzaparin). Low molecular weight heparins are at least as effective as low dose unfractionated heparin for preventing DVT and PE.
Fondaparinux 2.5 mg sc once/day is as effective as low molecular weight heparin for orthopedic surgery and in some other settings. It is a selective factor Xa inhibitor.
Warfarin is usually effective and safe at a dose of 2 to 5 mg orally once a day or at a dose adjusted to maintain an INR of 2 to 3 in patients who have undergone total hip or knee replacement. It is still used by some orthopedic surgeons for prophylaxis in these patients but is increasingly being supplanted by the use of the direct oral anticoagulants.
Rivaroxaban, an oral factor Xa inhibitor, is used for prevention of acute DVT/PE in patients undergoing total knee or hip arthroplasty. The dose is 10 mg orally once a day. Its use in other patients (surgical and nonsurgical) is currently under investigation.
Apixaban, an oral factor Xa inhibitor, is also used for prevention of acute DVT/PE in patients undergoing total knee or hip arthroplasty. The dose is 2.5 mg orally twice a day. Like rivaroxaban, its use in other types of patients is currently under investigation.

General material and educational and methodological support of the lecture:
- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:
1) Definition of pulmonary embolism.

2) Etiology factors for pulmonary embolism.
3) Pathogenesis of pulmonary embolism.
4) Symptoms of pulmonary embolism.
5) Diagnosis of pulmonary embolism.
6) Treatment of pulmonary embolism.
7) Maintenance anticoagulation
8) Prognosis for pulmonary embolism.

List of used sources:

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2. Davidson's Principles and Practice of Medicine: With Student Consult Online Access (Principles & Practice of Medicine (Davidson's)) 21st Edition
3. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Pulmonary-Embolism-Diagnosis-and-Management-of
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5. Young AM, Marshall A, Thirlwall J, et al : Comparison of an oral factor Xa inhibitor with LMWH in patients with cancer with VTE Results of a randomized trial (SELECT-D). J Clin Oncol 36 (20):2017–2029, 2018.
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Lecture № 6

Topic: Acquired heart defects

Actuality of theme: Valvular heart disease occurs as either a congenital or acquired condition and advances in medical care have resulted in valve disease becoming increasingly prevalent. Unfortunately, treatments remain inadequate due to our limited understanding of the genetic and molecular etiology of diseases affecting the heart valves. Therefore, surgical repair or replacement remains the most effective option, which comes with additional complications and no guarantee of life-long success. Over the past decade, there have been significant advances in our understanding of cardiac valve development and not surprisingly mutations in these developmental genes have been identified in humans with congenital valve malformations. Concurrently, there has been a greater realization that acquired valve disease is not simply a degenerative process. Molecular investigation of acquired valve disease has identified that numerous signaling pathways critical for normal valve development are re-expressed in diseased valves. This review will discuss recent advances in our understanding of the development of the heart valves along with the implications of these findings on the genetics of congenital and acquired valvular heart disease.

Goal: explain the essence of the acquired heart defects, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: acquired heart defects, mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis	 II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

	h. Criteria for the severity of disease i. Treatment j. Prevention	II II II		
III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Mitral regurgitation (MR) is incompetency of the mitral valve causing flow from the left ventricle (LV) into the left atrium during ventricular systole.

Etiology of Mitral Regurgitation

Mitral regurgitation may be

- Acute or chronic
- Primary or secondary

Causes of acute mitral regurgitation include

- Ischemic papillary muscle dysfunction or rupture
- Infective endocarditis with rupture of the chordae tendineae
- Acute rheumatic fever
- Myxomatous rupture of the chordae tendineae
- Acute dilation of the left ventricle due to myocarditis or myocardial ischemia
- Mechanical failure of a prosthetic mitral valve

Common causes of chronic mitral regurgitation are intrinsic valve pathology (primary MR) or distortion of a normal valve by dilatation and impairment of the left ventricle and/or the mitral annulus (secondary MR).

Primary MR pathology is most often mitral valve prolapse or rheumatic heart disease . Less common causes are connective tissue disorders, congenital cleft mitral valve, and radiation heart disease.

Secondary MR occurs when a disease of the left ventricle and atrium impairs valve function. Ventricular impairment and dilation displace the papillary muscles, which tether the otherwise normal leaflets and prevent them from closing fully. The causes are myocardial infarction (ischemic chronic secondary MR) or intrinsic myocardial disease (nonischemic chronic secondary MR). A less common mechanism is annular dilatation due to chronic atrial fibrillation with left atrial enlargement. In the presence of cardiomyopathy , any degree of secondary MR worsens prognosis.

In infants, the most likely causes of MR are papillary muscle dysfunction, endocardial fibroelastosis, acute myocarditis, cleft mitral valve with or without an endocardial cushion defect, and myxomatous degeneration of the mitral valve. MR may coexist with mitral stenosis when thickened valvular leaflets do not close.

Pathophysiology of Mitral Regurgitation

Acute mitral regurgitation may cause acute pulmonary edema and cardiogenic

shock or sudden cardiac death.

Complications of chronic MR include gradual enlargement of the left atrium (LA); LV enlargement and eccentric hypertrophy, which initially compensates for regurgitant flow (preserving forward stroke volume) but eventually decompensates (reducing forward stroke volume); atrial fibrillation (AF), which may be further complicated by thromboembolism; and infective endocarditis.

Symptoms and Signs of Mitral Regurgitation. Acute mitral regurgitation causes the same symptoms and signs as acute heart failure (dyspnea, fatigue, weakness, edema) and cardiogenic shock (hypotension with resultant multisystem organ damage). Specific signs of mitral regurgitation may be absent.

Chronic mitral regurgitation in most patients is initially asymptomatic, and symptoms develop insidiously as the LA enlarges, pulmonary artery pressure and venous pressure increase, and LV compensation fails. Symptoms include dyspnea, fatigue (due to heart failure), orthopnea, and palpitations (often due to atrial fibrillation). Rarely, patients present with endocarditis (eg, fever, weight loss, embolic phenomena).

Signs develop only when mitral regurgitation becomes moderate to severe. Inspection and palpation may detect a brisk apical impulse and sustained left parasternal movement due to systolic expansion of an enlarged LA. An LV impulse that is sustained, enlarged, and displaced downward and to the left suggests LV hypertrophy and dilation. A diffuse precordial lift occurs with severe MR because the LA enlarges, causing anterior cardiac displacement, and pulmonary hypertension causes right ventricular hypertrophy. A regurgitant murmur (or thrill) may also be palpable in severe cases.

On **auscultation,** the 1st heart sound (S1) may be soft (or occasionally loud). A 3rd heart sound (S3) at the apex reflects a dilated LV and severe MR.

The cardinal sign of mitral regurgitation is a holosystolic (pansystolic) murmur, heard best at the apex with the diaphragm of the stethoscope when the patient is in the left lateral decubitus position. In mild MR, the systolic murmur may be abbreviated or occur late in systole.

The murmur begins with S1 in conditions causing leaflet incompetency throughout systole, but it often begins after S1 (eg, when chamber dilation during systole distorts the valve apparatus or when myocardial ischemia or fibrosis alters dynamics). When the murmur begins after S1, it always continues to the 2nd heart sound (S2). The murmur radiates toward the left axilla; intensity may remain the same or vary. If intensity varies, the murmur tends to crescendo in volume up to S2.

MR murmurs increase in intensity with handgrip or squatting because peripheral vascular resistance to ventricular ejection increases, augmenting regurgitation into the LA; murmurs decrease in intensity with standing or the Valsalva maneuver. A short rumbling mid-diastolic inflow murmur due to torrential mitral diastolic flow may be heard following an S3. In patients with posterior leaflet prolapse, the murmur may be coarse and radiate to the upper sternum, mimicking aortic stenosis.

Diagnosis of Mitral Regurgitation

- Echocardiography

Diagnosis of mitral regurgitation is suspected clinically and confirmed by echocardiography . Doppler echocardiography is used to detect regurgitant flow and pulmonary hypertension. Two-dimensional or 3-dimensional echocardiography is used to determine the cause and severity of, the presence and extent of annular calcification, and the size and function of the LV and LA and to detect pulmonary hypertension. When it is acute, severe MR may not be apparent on color Doppler echocardiography, but suspicion is raised when acute heart failure is accompanied by hyperdynamic LV systolic function.

If endocarditis or valvular thrombi are suspected, **transesophageal echocardiography** (TEE) can provide a more detailed view of the mitral valve and LA. TEE is also indicated when mitral valve repair instead of replacement is being considered to evaluate the mechanism of MR in more detail.

An ECG and chest x-ray are usually obtained initially.

ECG may show LA enlargement and LV hypertrophy with or without ischemia. Sinus rhythm is usually present when MR is acute because the atria have not had time to stretch and remodel.

Chest x-ray in acute MR may show pulmonary edema; abnormalities in cardiac silhouette are not evident unless an underlying chronic disorder is also present. Chest x-ray in chronic MR may show LA and LV enlargement. It may also show pulmonary vascular congestion and pulmonary edema with heart failure.

Cardiac catheterization is done before surgery, mainly to determine whether coronary artery disease (CAD) is present. A prominent systolic *c-v* wave is seen on pulmonary artery occlusion pressure (pulmonary capillary wedge pressure) tracings during ventricular systole. Ventriculography can be used to quantify MR. Cardiac MRI can accurately measure regurgitant fraction and determine the cause of dilated myopathy with MR.

Periodic **exercise testing** (stress ECG) is often done to detect any decrease in effort tolerance, which would prompt consideration of surgical intervention. Periodic echocardiography is done to detect progression of MR.

Treatment of Mitral Regurgitation

- Mitral valve repair preferred for primary MR
- Medical therapy or mitral valve replacement for secondary MR
- Anticoagulants for patients with atrial fibrillation

Angiotensin-converting enzyme (ACE) inhibitors and other vasodilators do not delay LV dilation or MR progression and so have no role in asymptomatic MR with preserved LV function. However, if LV dilation or dysfunction is present, drug therapy using an angiotensin receptor blocker, neprilysin inhibitor (eg, sacubitril), aldosterone antagonist, and/or vasodilating beta-blocker (eg, carvedilol) is indicated. In secondary MR, these drugs can reduce the severity of MR and probably improve prognosis.

If the ECG shows left bundle branch block, then biventricular pacing may be beneficial for secondary MR.

Loop diuretics such as furosemide are helpful in patients with exertional or nocturnal

dyspnea. Digoxin may reduce symptoms in patients with AF or those in whom valve surgery is not appropriate.
Antibiotic prophylaxis is no longer recommended except for patients who have had valve replacement or repair utilizing prosthetic materials.
Anticoagulants are used to prevent thromboemboli in patients with AF.

Timing of intervention. **Acute mitral regurgitation** requires emergency mitral valve repair or replacement with concomitant coronary revascularization as necessary. Pending surgery, nitroprusside or nitroglycerin infusion and an intra-aortic ballon pump may be used to reduce afterload, thus improving forward stroke volume and reducing ventricular and regurgitant volume. **Chronic primary mitral regurgitation** that is severe needs intervention at the onset of symptoms or decompensation (LVEF $\leq$ 60% or LV end-systolic diameter $\geq$ 40 mm). Even in the absence of these triggers, intervention may be beneficial when surgical risk is low and valve morphology suggests a high likelihood of successful repair. Previous indications for intervention that are not in the latest guideline (1) include AF, pulmonary hypertension, flail leaflet, and left atrial dilation. When the EF falls to < 30%, surgical risk is high, necessitating a careful weighing of risk and benefit.
Chronic secondary mitral regurgitation has fewer indications for intervention. Because the primary pathology involves the LV muscle, correction of MR is not as beneficial and should be considered only when significant symptoms persist despite a trial of guideline-directed medical therapy, including biventricular pacing, if indicated. However, guidelines still weakly support (ie, class IIb recommendation) consideration of mitral valve surgery with either repair (with annuloplasty ring) or replacement if the patient has severe symptomatic mitral regurgitation with persistent NYHA (New York Heart Association) class III or IV symptoms . Indications for transcatheter edge-to-edge repair (TEER) are more permissive.
For patients undergoing cardiac surgery for other indications, concomitant mitral valve surgery should be considered for a repairable valve with MR that is moderate. However, for secondary MR, this practice has been questioned by the 2-year outcome of a recent randomized comparison with CABG alone. The addition of mitral valve repair did not affect LV remodelling or survival, but an excess of adverse events occurred (2). Therefore, only severe secondary MR should be treated when coronary artery bypass grafting (CABG) is being done for ischemia.

Mitral stenosis is narrowing of the mitral orifice that impedes blood flow from the left atrium to the left ventricle. In mitral stenosis, mitral valve leaflets become thickened and immobile and the mitral orifice becomes narrowed due to fusion of the commissures and the presence of shortened, thickened and matted chordae.
The **most common cause** is rheumatic fever, even though many patients do not recall the disorder. Women comprise 80% of cases. In regions with high prevalence of rheumatic fever, patients often present by age 30, usually with commissural fusion of pliable, noncalcified leaflets. In regions with low prevalence, patients typically present between ages 50 and 70 and with calcified fibrotic leaflets with subvalvular involvement in addition to commissural fusion.

A rare but increasing cause occurs in older patients with mitral annular calcification with extension of calcification into the leaflets, causing them to stiffen and not open fully. Occasionally, mitral stenosis is congenital or occurs after radiation therapy. If the valve cannot close completely, mitral regurgitation (MR) may coexist with mitral stenosis. Patients with mitral stenosis due to rheumatic fever may also have lesions of the aortic or tricuspid valve or both.

Left atrial (LA) size and pressure increase progressively to compensate for mitral stenosis; pulmonary venous and capillary pressures also increase and may cause secondary pulmonary hypertension, leading to right ventricular (RV) heart failure, tricuspid regurgitation, and pulmonic regurgitation. Rate of progression varies.

LA enlargement predisposes to atrial fibrillation (AF), a risk factor for thromboembolism. The faster heart rate and loss of atrial contraction with onset of AF often lead to sudden worsening of symptoms.

Symptoms and Signs of Mitral Stenosis correlate poorly with disease severity because the disease often progresses slowly, and patients unconsciously reduce their activity. Many patients are asymptomatic until they become pregnant or AF develops. Initial symptoms are usually those of heart failure (eg, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue).

Symptoms typically do not appear until 15 to 40 years after an episode of rheumatic fever. In medically underserved countries, young children may become symptomatic because streptococcal infections may not be treated with antibiotics and recurrent infections are common.

Paroxysmal or chronic atrial fibrillation further reduces blood flow into the left ventricle (LV), precipitating pulmonary edema and acute dyspnea when ventricular rate is poorly controlled. AF may also cause palpitations. In up to 15% of patients not taking anticoagulants, it causes systemic embolism with symptoms of stroke or other organ ischemia.

Less common symptoms include hemoptysis due to rupture of small pulmonary vessels and pulmonary edema, particularly during pregnancy when blood volume increases. Hoarseness due to compression of the left recurrent laryngeal nerve by a dilated LA or pulmonary artery (Ortner syndrome) and symptoms of pulmonary hypertension and RV failure may also occur.

Mitral stenosis may cause signs of cor pulmonale . The classic facial appearance in mitral stenosis, a plum-colored malar flush, occurs only when cardiac output is low and pulmonary hypertension is severe; cause is cutaneous vasodilation and chronic hypoxemia.

Occasionally, the initial symptoms and signs of mitral stenosis are those of an embolic event such as stroke. Endocarditis is rare in mitral stenosis unless mitral regurgitation is also present.

Palpation may detect palpable 1st and 2nd heart sounds (S1 and S2). S1 is best palpated at the apex, and S2 at the upper left sternal border. The pulmonic component of S2 (P2) is responsible for the impulse and results from pulmonary hypertension. An RV impulse (heave) palpable at the left sternal border may accompany jugular

venous distention when pulmonary hypertension is present and RV diastolic dysfunction develops.

Auscultation

- Loud S1
- Early diastolic opening snap
- Low-pitched decrescendo-crescendo rumbling diastolic murmur

Auscultatory findings in mitral stenosis include a loud S1 caused by the leaflets of a stenotic mitral valve closing abruptly (M1); it is heard best at the apex. S1 may be absent when the valve is heavily calcified and immobile. A normally split S2 with an exaggerated P2 due to pulmonary hypertension is also heard. Most prominent is an early diastolic opening snap as the leaflets billow into the LV, which is loudest close to left lower sternal border; it is followed by a low-pitched decrescendo-crescendo rumbling diastolic murmur, heard best with the bell of the stethoscope at the apex (or over the palpable apex beat) at end-expiration when the patient is in the left lateral decubitus position. The opening snap may be soft or absent if the mitral valve is calcified; the snap moves closer to S2 (increasing duration of the murmur) as mitral stenosis becomes more severe and LA pressure increases.

The diastolic murmur increases after a Valsalva maneuver (when blood pours into the LA), after exercise, and in response to maneuvers that increase afterload (eg, squatting, isometric handgrip). The murmur may be softer or absent when an enlarged RV displaces the LV posteriorly and when other disorders (pulmonary hypertension, right-sided valve abnormalities, AF with fast ventricular rate) decrease blood flow across the mitral valve. The presystolic crescendo is caused by increased flow with atrial contraction. However, the closing mitral valve leaflets during LV contraction may also contribute to this finding but only at the end of short diastoles when LA pressure is still high.

Diagnosis of Mitral Stenosis

- Echocardiography

Diagnosis of mitral stenosis is suspected clinically and confirmed by echocardiography . Typically, 2-dimensional echocardiography shows abnormal valve and subvalvular structures. It also provides information about the degree of valvular calcification and stenosis and LA size. Doppler echocardiography provides information about the transvalvular gradient and pulmonary artery pressure. The normal area of the mitral valve orifice is 4 to 5 cm^2.

Severity of mitral stenosis is characterized echocardiographically as

- Moderate: Valve area > 1.5 to 2.5 cm^2 or diastolic pressure half-time < 150 msec
- Severe: Valve area ≤ 1.5 cm^2 or diastolic pressure half-time ≥ 150 msec; symptoms are often present

However, the relationship between the area of the valve orifice and symptoms is not always consistent. Color Doppler echocardiography detects associated MR. Transesophageal echocardiography can be used to detect or exclude small LA thrombi, especially those in the LA appendage, which usually cannot be seen transthoracically. Transesophageal echocardiography also can better assess mitral regurgitation when mitral calcification causes acoustic shadowing of the left atrium.

The **ECG** may show LA enlargement, manifest as a P wave lasting > 0.12 msec with prominent negative deflection of its terminal component (duration: > 0.04 msec; amplitude: > 0.10 mV) in V1; broad, notched P waves in lead II; or both. Right axis QRS deviation and tall R waves in V1 suggest RV hypertrophy.

Chest x-ray usually shows straightening of the left cardiac border due to a dilated LA appendage, and widening of the carina. With barium in the esophagus, the lateral chest x-ray will show the dilated LA displacing the esophagus posteriorly. The main pulmonary artery (trunk) may be prominent; the descending right pulmonary artery diameter is ≥ 16 mm if pulmonary hypertension is significant. The upper lobe pulmonary veins may be dilated. A double shadow of an enlarged LA may be seen along the right cardiac border. Horizontal lines in the lower posterior lung fields (Kerley B lines) indicate interstitial edema associated with high LA pressure.

Exercise testing helps quantify symptoms. Further information can be obtained from stress echocardiography evaluation of changes in valve gradient and pulmonary pressure.

Cardiac catheterization , indicated only for perioperative assessment of coronary artery disease (CAD) before surgical repair, can confirm elevated LA and pulmonary artery pressures, mitral gradient and valve area.

Treatment of Mitral Stenosis

- Diuretics and sometimes beta-blockers or calcium channel blockers
- Anticoagulation for AF
- Commissurotomy or valve replacement

Asymptomatic patients with mitral stenosis require no treatment other than appropriate prophylaxis against rheumatic fever recurrence. Surveillance with serial TTE is important, because RV enlargement and rise in RV systolic pressure can occur without patients noticing a change in functional state, and without a decrease in mitral valve area. Early intervention may relieve pulmonary hypertension before it becomes permanent.

Mildly symptomatic patients usually respond to diuretics and, if sinus tachycardia or AF is present, to beta-blockers or calcium channel blockers, which can control ventricular rate.

Anticoagulation with a vitamin K antagonist (not a direct-acting oral anticoagulant [DOAC]) is indicated to prevent thromboembolism if patients have or have had AF, embolism, or a left atrial clot. Extended restoration of sinus rhythm is rarely possible. Anticoagulation may be considered in the presence of dense spontaneous contrast or an enlarged left atrium (M-mode diameter > 50 mm), but there are no good data to support this practice. All patients should be encouraged to continue at least low levels of physical exercise despite exertional dyspnea.

Antibiotic prophylaxis against endocarditis is no longer recommended except for patients who have had valve replacement.

Timing of intervention. **Moderate mitral stenosis** intervention may be indicated when cardiac surgery is required for other indications. Patients who are symptomatic and have exercise-induced mean transmitral gradient > 15 mm Hg or pulmonary capillary occlusion pressure > 25 mm Hg may be considered for percutaneous balloon

commissurotomy. **Severe mitral stenosis** intervention is indicated when any symptoms are present if the valve is suitable for percutaneous balloon commissurotomy (may be considered in asymptomatic patients if pulmonary pressure is > 50 mm Hg or there is new onset AF). Cardiac surgery is only pursued when symptoms are severe and for patients who are not candidates for percutaneous balloon commissurotomy or require other cardiac operations or do not have access to the percutaneous procedure.

Aortic regurgitation (AR) is incompetency of the aortic valve causing backflow from the aorta into the left ventricle during diastole.

Etiology of Aortic Regurgitation

Aortic regurgitation may be acute (very uncommonly) or chronic.

The primary causes of **acute aortic regurgitation** are

- Dissection of the ascending aorta
- Infective endocarditis

The primary causes of **chronic aortic regurgitation in adults** are

- Degeneration of the aortic valve and root (with or without a bicuspid valve)
- Infective endocarditis
- Myxomatous degeneration
- Rheumatic fever
- Thoracic aortic aneurysm
- Trauma

The most common cause of **chronic aortic regurgitation in children** is

- Ventricular septal defect with aortic valve prolapse

Rarely, aortic regurgitation is caused by seronegative spondyloarthropathies (ankylosing spondylitis , reactive arthritis , psoriatic arthritis), rheumatoid arthritis , systemic lupus erythematosus , arthritis associated with ulcerative colitis , luetic (syphilitic) aortitis, osteogenesis imperfecta , supravalvular or discrete membranous subaortic stenosis, Takayasu arteritis , rupture of a sinus of Valsalva, acromegaly , and giant cell arteritis . Aortic regurgitation due to myxomatous degeneration may develop in patients with Marfan syndrome or Ehlers-Danlos syndrome.

Symptoms and Signs of Aortic Regurgitation. Acute aortic regurgitation causes symptoms of heart failure (dyspnea, fatigue, weakness, edema) and cardiogenic shock (hypotension with resultant multisystem organ damage).

Chronic aortic regurgitation is typically asymptomatic for years; progressive exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitations develop insidiously.

Symptoms of heart failure correlate poorly with objective measures of left ventricular function. Chest pain (angina pectoris) affects only about 5% of patients who do not have coexisting coronary artery disease (CAD) and, when it occurs, is especially common at night. Patients may present with endocarditis (eg, fever, anemia, weight loss, embolic phenomena) because the abnormal aortic valve is predisposed to bacterial seeding.

Signs vary by severity and acuity. Signs in acute aortic regurgitation reflect heart failure and cardiogenic shock and typically include tachycardia, cool extremities, lung crackles, and low blood pressure (BP). The 1st heart sound (S1) is usually absent

(because aortic and LV diastolic pressures equalize), and a 3rd heart sound (S3) is common. An AR murmur may be absent even if AR is severe, although an Austin Flint murmur is common.

As chronic disease progresses, systolic blood pressure increases while diastolic blood pressure decreases, creating a widened pulse pressure. With time, the LV impulse may become enlarged, increased in amplitude, and displaced downward and laterally, with systolic depression of the entire left parasternal area, giving a rocking motion to the left chest.

A systolic apical or carotid thrill may become palpable in later stages of AR; it is caused by large forward stroke volumes and low aortic diastolic pressure.

Auscultatory findings include a normal S1 and a nonsplit, loud, sharp or slapping 2nd heart sound (S2) caused by increased elastic aortic recoil. The murmur of AR is often unimpressive. The murmur is blowing, high-pitched, diastolic, and decrescendo, beginning soon after the aortic component of S2 (A2); it is loudest at the 3rd or 4th left parasternal intercostal space. The murmur is heard best with the diaphragm of the stethoscope when the patient is leaning forward, with breath held at end-expiration. It increases in volume in response to maneuvers that increase afterload (eg, squatting, isometric handgrip). If AR is slight, the murmur may occur only in early diastole. If LV diastolic pressure is very high, the murmur is short because aortic and LV diastolic pressures equalize earlier in diastole.

Palpable signs include a large-volume pulse with rapid rise and fall (slapping, water-hammer, or collapsing pulse) and pulsation of the carotid arteries (Corrigan sign), retinal arteries (Becker sign), liver (Rosenbach sign), or spleen (Gerhard sign). BP findings may include popliteal systolic pressure ≥ 60 mm Hg higher than brachial pressure (Hill sign) and a fall in diastolic BP of > 15 mm Hg with arm elevation (Mayne sign). Auscultatory signs include a sharp sound heard over the femoral pulse (pistol-shot sound, or Traube sign) and a femoral systolic bruit distal and a diastolic bruit proximal to arterial compression (Duroziez sign).

Diagnosis of Aortic Regurgitation

- Echocardiography

Diagnosis of aortic regurgitation is suspected based on history and physical examination findings and confirmed by echocardiography . Doppler echocardiography is the test of choice to detect and quantify the magnitude of regurgitant blood flow and grade overall severity of the AR. Two-dimensional echocardiography can quantify aortic root size and anatomy and LV function.

Severe chronic aortic regurgitation is suggested by any of the following:

- Color Doppler jet width $\geq 65\%$ of the LV outflow tract diameter
- Holodiastolic flow reversal in the abdominal aorta (specific for severe AR)
- Regurgitant volume ≥ 60 mL/beat
- Regurgitation fraction $\geq 50\%$
- Vena contracta > 6 mm (the narrowest diameter of the fluid stream downstream of the abnormal valve orifice)

Echocardiography can also assess severity of pulmonary hypertension secondary to

LV failure, detect vegetations or pericardial effusions (eg, in aortic dissection), and provide information about prognosis. Coarctation is associated with bicuspid valve and is detected by placing the ultrasound transducer at the suprasternal notch. Transesophageal echocardiography provides additional delineation of aortic dilatation and valve anatomy, which is especially useful when surgical repair is being considered. If the aorta is enlarged, gated CT or MRI is recommended to evaluate the entire thoracic aorta. MRI also can help assess LV function and degree of AR when echocardiographic images are suboptimal.

ECG and chest x-ray should be done.

ECG may show repolarization abnormalities with or without QRS voltage criteria of LV hypertrophy, left atrial enlargement, and T-wave inversion with ST-segment depression in precordial leads.

Chest x-ray may show cardiomegaly and a prominent aortic root in patients with chronic progressive AR. If AR is severe, signs of pulmonary edema and HF may also be present. Exercise testing may help assess functional capacity and symptoms in patients with documented AR and equivocal symptoms.

Coronary angiography should be done before surgery, even if no angina is present because about 20% of patients with severe AR have significant CAD, which may need concomitant coronary artery bypass graft surgery.

First-degree relatives of patients with a bicuspid valve should be screened using echocardiography because 20 to 30% will be similarly affected.

Treatment of Aortic Regurgitation

- Aortic valve replacement or repair
- Sometimes vasodilators, diuretics, and nitrates

When aortic root dilatation is part of the mechanism of aortic regurgitation, angiotensin-receptor blockers may slow progression, making them favored drugs for patients with concomitant hypertension. These drugs do not reduce the severity of aortic regurgitation or alter disease progression.

Intervention is either surgical aortic valve replacement or (less commonly) valve repair. Percutaneous options are being developed. An aortic bioprosthetic valve requires anticoagulation for 3 to 6 months postoperatively, but a mechanical valve requires lifetime anticoagulation using warfarin. Direct oral anticoagulants (DOAC) are ineffective and should not be used. Patients who are not candidates for surgery benefit from treatment of HF (eg, with diuretics, vasodilators, nitrates). Beta-blockers should be used with caution because they block compensatory tachycardia and worsen AR by prolonging diastole. Intra-aortic balloon pump insertion is contraindicated because the diastolic balloon inflation worsens AR.

Patients with severe AR who do not meet the criteria for intervention should be reevaluated by physical examination and echocardiography every 6 to 12 months.

Antibiotic prophylaxis against endocarditis is no longer recommended for aortic regurgitation except for patients who have had valve replacement.

Criteria for intervention

Intervention is indicated when

- AR is severe and is causing symptoms

- AR is severe and is causing LV dysfunction (EF ≤ 55%, LV end-systolic dimension > 50 mm, or indexed to body surface area > 25 mm/m^2)
- AR is severe and at least 3 serial studies show a progressive decline in EF to 55 to 60%, or progressive increase in LV end-diastolic dimension to > 65 mm

Patients with an **enlarged ascending aorta** frequently have AR as well as an increased risk of aortic dissection . A high risk of aortic dissection may be the first indication for cardiac surgery, which should be undertaken when

- Ascending aortic diameter is> 55 mm
- Bicuspid valve is present with ascending aortic diameter 50 to 55 mm and either aortic growth rate is > 5 mm/year, aortic coarctation is present, or there is a family history of aortic dissection
- Marfan syndrome is present with ascending aortic diameter > 50 mm (or less if the aortic growth rate is > 5 mm/year or there is a family history of aortic dissection at < 50 mm diameter

When cardiac surgery is being done for other reasons, concomitant aortic surgery is indicated if the ascending aortic diameter is ≥ 45 mm

Aortic stenosis (AS) is narrowing of the aortic valve, obstructing blood flow from the left ventricle to the ascending aorta during systole.

Etiology of Aortic Stenosis

In older patients, the most common precursor to aortic stenosis is

- Aortic sclerosis

Aortic sclerosis is a degenerative aortic valve disease with thickening of aortic valve structures by fibrosis and calcification initially without causing significant obstruction. Over years, aortic sclerosis progresses to stenosis in as many as 15% of patients. Aortic sclerosis resembles atherosclerosis , with deposition of lipoproteins and inflammation and calcification of the valves; risk factors are similar: lipoprotein (a) is implicated in the pathogenesis of both aortic stenosis and atherosclerosis. Elevated lipoprotein (a) levels also predict faster hemodynamic progression of AS. Patients with psoriasis are at increased risk for atherosclerosis, and more recently, psoriasis has been tied to an increased risk of aortic stenosis.

In patients < 70 years, the most common cause of aortic stenosis is

- A congenital bicuspid aortic valve

Congenital aortic stenosis occurs in 3 to 5/1000 live births and affects more males; it is associated with coarctation and progressive dilatation of the ascending aorta, causing aortic dissection .

In medically underserved countries, the most common cause of aortic stenosis in all age groups is

- Rheumatic fever

Supravalvular AS caused by a discrete congenital membrane or hypoplastic constriction just above the sinuses of Valsalva is uncommon. A sporadic form of supravalvular AS is associated with a characteristic facial appearance (high and broad forehead, hypertelorism, strabismus, upturned nose, long philtrum, wide mouth, dental abnormalities, puffy cheeks, micrognathia, low-set ears). When associated with idiopathic hypercalcemia of infancy , this form is known as Williams syndrome.

Subvalvular AS caused by a congenital membrane or fibrous ring just beneath the aortic valve is uncommon.

Symptoms and Signs of Aortic Stenosis

Congenital aortic stenosis is usually asymptomatic until age 10 or 20 years, when symptoms develop insidiously. In all forms, progressive untreated aortic stenosis ultimately results in exertional syncope, angina, and dyspnea (SAD triad). Other symptoms and signs may include those of heart failure and arrhythmias , including ventricular fibrillation leading to sudden death.

Exertional syncope occurs because cardiac output cannot increase enough to meet the demands of physical activity. Nonexertional syncope may result from altered baroreceptor responses or ventricular tachycardia . Exertional angina pectoris affects about two thirds of patients; about half have significant coronary artery atherosclerosis, and half have normal coronary arteries but have ischemia induced by LV hypertrophy and altered coronary flow dynamics.

There are no visible signs of aortic stenosis. Palpable signs include carotid and peripheral pulses that are reduced in amplitude and slow rising (pulsus parvus et tardus) and an apical impulse that is sustained (thrusts with the 1st heart sound [S1] and relaxes with the 2nd heart sound [S2]) because of left ventricular hypertrophy. The LV impulse may become displaced when systolic dysfunction develops. A palpable 4th heart sound (S4), felt best at the apex, and a systolic thrill, corresponding with the murmur of AS and felt best at the left upper sternal border, are occasionally present in severe cases. Systolic blood pressure (BP) may be high even when AS is severe but ultimately falls when the LV fails.

On **auscultation**, S1 is normal and S2 is single because aortic valve closing is delayed and merges with the pulmonic (P2) component of S2. The aortic component may also be soft. Paradoxical splitting of S2 may be heard. A normally split S2 is the only physical finding that reliably excludes severe AS. An S4 may be audible. An ejection click may also be audible early after S1 in patients with congenital bicuspid AS when valve leaflets are stiff but not completely immobile. The click does not change with dynamic maneuvers.

The hallmark finding is a crescendo-decrescendo ejection murmur, heard best with the diaphragm of the stethoscope at the right and left upper sternal border when a patient who is sitting upright leans forward. The murmur typically radiates to the right clavicle and both carotid arteries (left often louder than right) and has a harsh or grating quality. But in older patients, vibration of the unfused cusps of calcified aortic valve leaflets may transmit a louder, more high-pitched, “cooing” or musical sound to the cardiac apex, with softening or absence of the murmur parasternally (Gallavardin phenomenon), thereby mimicking mitral regurgitation. The murmur is soft when stenosis is less severe, grows louder as stenosis progresses, and becomes longer and peaks in volume later in systole (ie, crescendo phase becomes longer and decrescendo phase becomes shorter) as stenosis becomes more severe. As LV contractility decreases in critical AS, the murmur becomes softer and shorter. The intensity of the murmur may therefore be misleading in these circumstances.

The murmur of aortic stenosis typically increases with maneuvers that increase LV

volume and contractility (eg, leg-raising, squatting, Valsalva release, after a ventricular premature beat) and decreases with maneuvers that decrease LV volume (Valsalva maneuver) or increase afterload (isometric handgrip). These dynamic maneuvers have the opposite effect on the murmur of hypertrophic cardiomyopathy, which can otherwise resemble that of AS. The murmur of mitral regurgitation due to prolapse of the posterior leaflet may also mimic AS.

Diagnosis of Aortic Stenosis

- Echocardiography

Diagnosis of aortic stenosis is suspected clinically and confirmed by echocardiography . Two-dimensional transthoracic echocardiography is used to identify a stenotic aortic valve and possible causes, to quantify LV hypertrophy and degree of systolic dysfunction, and to detect coexisting valvular heart disorders (aortic regurgitation, mitral valve disorders) and complications (eg, endocarditis). Doppler echocardiography is used to quantify degree of stenosis by measuring jet velocity, transvalvular systolic pressure gradient, and aortic valve area.

Severity of aortic stenosis is characterized echocardiographically as

- Mild: Peak aortic jet velocity 2 to 2.9 m/second or mean gradient < 20 mm Hg
- Moderate: Peak aortic jet velocity 3 to 4 m/second or mean gradient 20 to 40 mm Hg
- Severe: Peak aortic jet velocity > 4 m/second or mean gradient > 40 mm Hg
- Very severe: Peak aortic jet velocity > 5 m/second or mean gradient > 60 mm Hg

Clinical judgment and critical review of the data are used to resolve any discordance among these parameters (eg, moderate valve area but severe mean gradient). Measurement of aortic valve area is least accurate when LV volume or systolic function is reduced, or if systemic hypertension is present

The gradient may be overestimated when aortic regurgitation is present. The gradient may under-represent severity when the stroke volume is low, eg, in patients with systemic hypertension or LV systolic dysfunction (low-gradient AS with reduced EF) or a small, hypertrophied LV (low-gradient AS with normal EF. Sometimes LV systolic dysfunction results in low ventricular pressure that is inadequate to open nonstenotic valve leaflets, causing echocardiographic appearance of low valve area in the absence of stenosis (pseudostenosis). Differentiation of pseudostenosis from low-gradient AS can be aided by calculation of the ratio of outflow tract to aortic velocity (Doppler velocity index, DVI). A DVI value < 0.25 suggests true severe stenosis. Assessment of the degree of valve calcification by CT can help determine the severity of AS. Severe AS is likely when the valvular calcium score is > 2000 (men) and > 1300 (women). It is very likely when the calcium score is > 3000 (men) and > 1600 (women). Low-dose dobutamine stress echocardiography distinguishes low-gradient AS from pseudostenosis.

ECG typically shows changes of LV hypertrophy with or without an ischemic ST- and T-wave pattern.

Chest x-ray findings may include calcification of the aortic cusps (seen on the lateral

projection or on fluoroscopy) and evidence of heart failure. Heart size may be normal or only mildly enlarged.

In asymptomatic patients with severe aortic stenosis, closely supervised **exercise ECG testing** is recommended in an attempt to elicit symptoms of angina, dyspnea, or hypotension—any of these symptoms, when due to the AS, is an indication for intervention. Failure to normally increase BP and development of ST segment depression are less predictive of adverse prognosis. Exercise testing is contraindicated in symptomatic patients.

Treatment of Aortic Stenosis

- Sometimes aortic valve replacement

Nothing has yet been proved to slow the progression of aortic stenosis. In randomized trials, statin therapy has been ineffective.

Drugs that can cause hypotension (eg, nitrates) should be used cautiously, although nitroprusside has been used as a temporizing measure to reduce afterload in patients with decompensated heart failure in the hours before valve replacement. Patients who develop heart failure but are too high risk for valve intervention benefit from cautious treatment with digoxin, diuretics, and angiotensin-converting enzyme (ACE) inhibitors.

Timing of intervention

The benefits of intervention do not outweigh the risks until patients develop symptoms and/or meet certain echocardiographic criteria. Thus, patients should have periodic clinical evaluations, including echocardiography and sometimes exercise testing, to determine the optimal time for valve replacement. Valve replacement is recommended when aortic stenosis is severe and there is any one of the following:

- Symptoms
- Exercise testing causing symptoms or showing reduced effort tolerance or a fall in blood pressure ≥ 10 mm Hg below baseline)
- LV EF < 50%

If surgical risk is low, then surgery may be considered if there is any one of:

- Very severe AS (aortic velocity > 5 m/second)
- Brain (B-type) natriuretic peptide (BNP) is > 3 times normal
- Severe pulmonary hypertension without other explanation
- Decline in EF to < 60%
- Severe valve calcification with rapid progression of stenosis (reduction in aortic valve area ≥ 0.3 m/second/year)

When cardiac surgery is being done for other reasons, concomitant aortic valve surgery is indicated regardless of symptoms if the AS is moderate or greater.

Choice of intervention

Balloon valvotomy is used primarily in children and very young adults with congenital AS.

In older patients who are not candidates for surgery, **balloon valvuloplasty** has been used as a bridge to valve replacement but this procedure has a high complication rate and provides only temporary relief. It is being replaced by transcatheter valve implantation, which can be done with similar procedural risk, even in sick, high-risk

patients.

Surgical aortic valve replacement (SAVR) usually involves replacement with a mechanical or bioprosthetic valve, but in younger patients, the patient's own pulmonic valve can be used, with a bioprosthesis then used to replace the pulmonic valve (Ross procedure).

Transcatheter (percutaneous) aortic valve implantation (TAVI) (sometimes called transcatheter aortic valve replacement, or TAVR) is a less invasive method of aortic valve replacement for which the indications continue to expand.

General material and educational and methodological support of the lecture:

- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:

1) Etiology factors of mitral stenosis, mitral regurgitation.
2) Etiology factors of aortic stenosis, aortic regurgitation.
3) Sings and symptoms of mitral stenosis.
4) Sings and symptoms of mitral regurgitation.
5) Sings and symptoms of aortic stenosis.
6) Sings and symptoms of aortic regurgitation.
7) Diagnosis of aortic stenosis, aortic regurgitation.
8) Diagnosis of mitral stenosis, mitral regurgitation.
9) Treatment of aortic stenosis, aortic regurgitation.
10) Treatment of mitral stenosis, mitral regurgitation.

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Lecture № 7

Topic: Infective endocarditis

Actuality of theme: Infective endocarditis (IE) is a rare, life-threatening disease that has long-lasting effects even among patients who survive and are cured. IE disproportionately affects those with underlying structural heart disease and is increasingly associated with healthcare contact, particularly in patients who have intravascular prosthetic material. In the setting of bacteraemia with a pathogenic organism, an infected vegetation may form as the end result of complex interactions between invading microorganisms and the host immune system. Once established, IE can involve almost any organ system in the body. The diagnosis of IE may be difficult to establish and a strategy that combines clinical, microbiological and echocardiography results has been codified in the modified Duke criteria. In cases of blood culture-negative IE, the diagnosis may be especially challenging and novel microbiological and imaging techniques have been developed to establish its presence. Once diagnosed, IE is best managed by a multidisciplinary team with expertise in infectious diseases, cardiology and cardiac surgery. Antibiotic prophylaxis for the prevention of IE remains controversial. Efforts to develop a vaccine targeting common bacterial causes of IE are ongoing, but have not yet yielded a commercially available product.

Goal: explain the essence of the infective endocarditis, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: infective endocarditis, bacteraemia, valve disease, heart failure, vegetation, thrombosis, antibiotic.

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)

II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease i. Treatment j. Prevention	 II II II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)
III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

Endocarditis usually refers to infection of the endocardium (ie, infective endocarditis). The term can also include noninfective endocarditis, in which sterile platelet and fibrin thrombi form on cardiac valves and adjacent endocardium. Noninfective endocarditis sometimes leads to infective endocarditis. Both can result in embolization and impaired cardiac function.

The diagnosis of infective endocarditis is usually based on a constellation of clinical findings rather than a single definitive test result.

Etiology of Infective Endocarditis. The normal heart is relatively resistant to infection. Bacteria and fungi do not easily adhere to the endocardial surface, and constant blood flow helps prevent them from settling on endocardial structures. Thus, 2 factors are typically required for endocarditis:

- A predisposing abnormality of the endocardium
- Microorganisms in the bloodstream (bacteremia)

Rarely, massive bacteremia or particularly virulent microorganisms cause endocarditis on normal valves.

Endocardial factors. Endocarditis usually involves the heart valves. Major predisposing factors are congenital heart defects , rheumatic valvular disease , bicuspid or calcific aortic valves, mitral valve prolapse , hypertrophic cardiomyopathy , and prior endocarditis. Prosthetic valves and other intracardiac devices are a particular risk. Occasionally, mural thrombi, ventricular septal defects , and patent ductus arteriosus sites become infected. The actual nidus for infection is usually a sterile fibrin-platelet vegetation formed when damaged endothelial cells release tissue factor.

Infective endocarditis occurs most often on the left side (eg, mitral or aortic valve). About 10 to 20% of cases are right-sided (tricuspid or pulmonic valve). Intravenous drug abusers have a much higher incidence of right-sided endocarditis (about 30 to 70%).

Microorganisms that infect the endocardium may originate from distant infected sites (eg, cutaneous abscess, inflamed or infected gums, urinary tract infection) or have obvious portals of entry such as a central venous catheter or a drug injection site. Almost any implanted foreign material (eg, ventricular or peritoneal shunt, prosthetic device) is at risk of bacterial colonization, thus becoming a source of bacteremia and hence endocarditis. Endocarditis also may result from asymptomatic bacteremia, such as typically occurs during invasive dental, medical, or surgical procedures. Even toothbrushing and chewing can cause bacteremia (usually due to viridans streptococci) in patients with gingivitis.

Causative microorganisms vary by site of infection, source of bacteremia, and host risk factors (eg, IV drug abuse), but overall, streptococci and *Staphylococcus aureus* cause 80 to 90% of cases. Enterococci, gram-negative bacilli, HACEK organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), and fungi cause most of the rest.

The disease develops in 3 stages:

- Bacteremia: Microorganisms are present in the blood
- Adhesion: The microorganism adheres to abnormal or damaged endothelium via surface adhesions
- Colonization: Proliferation of the organism together with inflammation, leading to a mature vegetation

Many of the causative microorganisms produce polysaccharide biofilms that shield them from host immune defences and impede antibiotic penetration.

Pathophysiology of Infective Endocarditis. Endocarditis has local and systemic consequences.

Local consequences of infective endocarditis include

- Myocardial abscesses with tissue destruction and sometimes conduction system abnormalities (usually with low septal abscesses)
- Sudden, severe valvular regurgitation, causing heart failure and death (usually due to mitral or aortic valve lesions)
- Aortitis due to contiguous spread of infection

Prosthetic valve infections are particularly likely to involve valve ring abscesses, obstructing vegetations, myocardial abscesses, and mycotic aneurysms manifested by valve obstruction, dehiscence, and conduction disturbances.

Systemic consequences of endocarditis are primarily due to

- Embolization of infected material from the heart valve
- Immune-mediated phenomena (primarily in chronic infection)

Right-sided lesions typically produce septic pulmonary emboli, which may result in pulmonary infarction, pneumonia, or empyema. Left-sided lesions may embolize to any tissue, particularly the kidneys, spleen, and central nervous system. Mycotic aneurysms can form in any major artery. Cutaneous and retinal emboli are common.

Diffuse glomerulonephritis may result from immune complex deposition.

Classification of Infective Endocarditis Infective endocarditis may have an indolent, subacute course or a more acute, fulminant course with greater potential for rapid decompensation.

Subacute bacterial endocarditis (SBE), although aggressive, usually develops insidiously and progresses slowly (ie, over weeks to months). Often, no source of infection or portal of entry is evident. SBE is caused most commonly by streptococci (especially viridans, microaerophilic, anaerobic, and nonenterococcal group D streptococci and enterococci) and less commonly by *S. aureus*, *Staphylococcus epidermidis*, *Gemella morbillorum*, *Abiotrophia defectiva* (formerly, *Streptococcus defectivus*), *Granulicatella* species, and fastidious *Haemophilus* species. SBE often develops on abnormal valves after asymptomatic bacteremia due to periodontal, gastrointestinal, or genitourinary infections.

Acute bacterial endocarditis (ABE) usually develops abruptly and progresses rapidly (ie, over days). A source of infection or portal of entry is often evident. When bacteria are virulent or bacterial exposure is massive, ABE can affect normal valves. It is usually caused by *S. aureus*, group A hemolytic streptococci, pneumococci, or gonococci.

Prosthetic valvular endocarditis (PVE) develops in 2 to 3% of patients within 1 year after valve replacement and in 0.5%/year thereafter. It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally. Early-onset infections (< 2 months after surgery) are caused mainly by contamination during surgery with antimicrobial-resistant bacteria (eg, *S. epidermidis*, diphtheroids, coliform bacilli, *Candida* species, *Aspergillus* species). Late-onset infections are caused mainly by contamination with low-virulence organisms during surgery or by transient asymptomatic bacteremias, most often with streptococci; *S. epidermidis;* diphtheroids; and the fastidious gram-negative bacilli, *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, and *Cardiobacterium hominis*.

Symptoms and Signs of Infective Endocarditis vary based on the classification but are nonspecific.

Subacute bacterial endocarditis. Initially, symptoms of subacute bacterial endocarditis are vague: low-grade fever (< 39° C), night sweats, fatigability, malaise, and weight loss. Chills and arthralgias may occur. Symptoms and signs of valvular insufficiency may be a first clue. Initially, ≤ 15% of patients have fever or a murmur, but eventually almost all develop both. Physical examination may be normal or include pallor, fever, change in a preexisting murmur or development of a new regurgitant murmur, and tachycardia.

Retinal emboli can cause round or oval hemorrhagic retinal lesions with small white centers (Roth spots). Cutaneous manifestations include petechiae (on the upper trunk, conjunctivae, mucous membranes, and distal extremities), painful erythematous subcutaneous nodules on the tips of digits (Osler nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), and splinter hemorrhages under the nails. About 35% of patients have central nervous system (CNS) effects, including transient

ischemic attacks , stroke , toxic encephalopathy, and, if a mycotic CNS aneurysm ruptures, brain abscess and subarachnoid hemorrhage. Renal emboli may cause flank pain and, rarely, gross hematuria. Splenic emboli may cause left upper quadrant pain. Prolonged infection may cause splenomegaly or clubbing of fingers and toes.

Acute bacterial endocarditis and prosthetic valvular endocarditis. Symptoms and signs of acute bacterial endocarditis and prosthetic valvular endocarditis are similar to those of subacute bacterial endocarditis, but the course is more rapid. Fever is almost always present initially, and patients appear toxic; sometimes septic shock develops. Heart murmur is present initially in about 50 to 80% and eventually in > 90%. Rarely, purulent meningitis occurs.

Right-sided endocarditis. Septic pulmonary emboli may cause cough, pleuritic chest pain, and sometimes hemoptysis. A murmur of tricuspid regurgitation is typical.

Diagnosis of Infective Endocarditis

- Blood cultures
- Echocardiography and sometimes other imaging modalities
- Clinical criteria

Because symptoms and signs are nonspecific, vary greatly, and may develop insidiously, diagnosis requires a high index of suspicion. Endocarditis should be suspected in patients with fever and no obvious source of infection, particularly if a heart murmur is present. Suspicion of endocarditis should be very high if blood cultures are positive in patients who have a history of a heart valve disorder, who have had certain recent invasive procedures, or who abuse IV drugs. Patients with documented bacteremia should be examined thoroughly and repeatedly for new valvular murmurs and signs of emboli.

Other than positive blood cultures, there are no specific laboratory findings. Established infections often cause a normocytic-normochromic anemia, elevated white blood cell count, increased erythrocyte sedimentation rate, increased immunoglobulin levels, and the presence of circulating immune complexes and rheumatoid factor, but these findings are not diagnostically helpful. Urinalysis often shows microscopic hematuria and, occasionally, red blood cell casts, pyuria, or bacteriuria.

Identification of organisms and its antimicrobial susceptibility is vital to guide treatment.

If endocarditis is suspected, 3 blood samples for culture (20-mL each) should be obtained within 24 hours (if presentation suggests acute bacterial endocarditis, 2 cultures within the first 1 to 2 hours). Each set of cultures should be obtained from a separate, fresh venipuncture site (ie, not from preexisting vascular catheters). Blood cultures do not need to be done during chills or fever because most patients have continuous bacteremia. When endocarditis is present and no prior antibiotic therapy was given, all 3 blood cultures usually are positive because the bacteremia is continuous; at least one culture is positive in 99%. Premature use of empiric antibiotic therapy should be avoided in patients with acquired or congenital valvular or shunt lesions to avoid culture-negative endocarditis. If prior antimicrobial therapy was given, blood cultures should still be obtained, but results may be negative.

Blood cultures may require 3 to 4 weeks of incubation for certain organisms; however, some proprietary, automated culture monitoring systems can identify positive cultures within a week. Other organisms (eg, *Aspergillus*) may not produce positive cultures. Some organisms (eg, *Coxiella burnetii*, *Bartonella* species, *Chlamydia psittaci*, *Brucella* species) require serodiagnosis; others (eg, *Legionella pneumophila*) require special culture media or polymerase chain reaction (eg, *Tropheryma whippelii*). Negative blood culture results may indicate suppression due to prior antimicrobial therapy, infection with organisms that do not grow in standard culture media, or another diagnosis (eg, noninfective endocarditis, atrial myxoma with embolic phenomena, vasculitis).

Imaging studies. Echocardiography , typically transthoracic (TTE) rather than transesophageal (TEE), should be done initially. TEE is more sensitive (ie, capable of revealing vegetations too small to be seen on TTE).

Transesophageal echocardiography should be done when

- Patients have a prosthetic valve
- Transthoracic echocardiogram is nondiagnostic
- Diagnosis of infective endocarditis has been established clinically (done to detect perforations, abscesses, and fistulas)

CT is used occasionally when TEE fails to fully define paravalvular abscesses and for detection of mycotic aneurysms. Positron emission tomography (PET) scanning is an emerging tool for the diagnosis of endocarditis originating in prosthetic and intracardiac devices. CT and PET abnormalities are now included as major criteria in the European guidelines.

Diagnostic criteria. Infective endocarditis is definitively diagnosed when microorganisms are seen histologically in (or cultured from) endocardial vegetations obtained during cardiac surgery, embolectomy, or autopsy. Because vegetations are not usually available for examination, there are various clinical criteria for establishing a diagnosis. They include the revised Duke Criteria (with a sensitivity and specificity > 90%—see tables Diagnostic Requirements for Infective Endocarditis and Revised Duke Clinical Diagnostic Criteria for Infective Endocarditis) and the European Society of Cardiology (ESC) 2015 modified criteria.

The ESC criteria are similar to the modified Duke criteria but include expanded imaging results as major criteria as follows:

- Vegetation, abscess, pseudoaneurysm, intracardiac fistula, valvular perforation or aneurysm, or new partial dehiscence of prosthetic valve identified by echocardiography
- Abnormal activity around a prosthetic valve (implanted > 3 months earlier) detected by PET/CT or single-photon emission computed tomography (SPECT)/CT with radiolabeled leukocytes
- Paravalvular lesions identified by cardiac CT

The ESC also differs from the modified Duke minor criteria by specifying that detecting silent vascular phenomena by imaging only is sufficient.

Prognosis for Infective Endocarditis. Untreated, infective endocarditis is always

fatal. Even with treatment, death is more likely and the prognosis is generally poorer for older people and people who have

- Infection with resistant organisms
- An underlying disorder
- A long delay in treatment
- Aortic valve or multiple valve involvement
- Large vegetations
- Polymicrobial bacteremia
- Prosthetic valve infections
- Mycotic aneurysms
- Valve ring abscess
- Major embolic events

Septic shock is more likely in patients with diabetes, acute renal insufficiency, *S. aureus* infection, vegetation size > 15 mm, and signs of persistent infection. The mortality rate for viridans streptococcal endocarditis without major complications is < 10% but is virtually 100% for *Aspergillus* endocarditis after prosthetic valve surgery.

The prognosis is better with right-sided than left-sided endocarditis because tricuspid valve dysfunction is tolerated better, systemic emboli are absent, and right-sided *S. aureus* endocarditis responds better to antimicrobial therapy

Treatment of Infective Endocarditis

- IV antibiotics (based on the organism and its susceptibility)
- Sometimes valve debridement, repair, or replacement
- Dental evaluation and treatment (to minimize oral sources of bacteremia)
- Removal of potential source of bacteremia (eg, internal catheters, devices)

Treatment consists of a prolonged course of antimicrobial therapy (1). Surgery may be needed for mechanical complications or resistant organisms. Typically, antimicrobials are given IV. Because they must be given for 2 to 8 weeks, home IV therapy is often used.

Any apparent source of bacteremia must be managed: necrotic tissue debrided, abscesses drained, and foreign material and infected devices removed. People with infective endocarditis should be evaluated by a dentist and treated for oral diseases that could cause bacteremia and subsequent endocarditis. Existing IV catheters (particularly central venous ones) should be changed. If endocarditis persists in a patient with a newly inserted central venous catheter, that catheter should also be removed. Organisms within biofilms adherent to catheters and other devices may not respond to antimicrobial therapy, leading to treatment failure or relapse. If continuous infusions are used instead of intermittent boluses, infusions should not be interrupted for long periods.

Antibiotic regimens. Drugs and dosages depend on the microorganism and its antimicrobial susceptibility.

Although most patients are stable enough to wait for culture results, empiric antibiotic therapy before organism identification may be necessary in seriously ill patients. *An-*

tibiotics should not be given until adequate blood cultures (2 or 3 samples from different sites over 1 hour) have been obtained. Antibiotics should be broad spectrum to cover all likely organisms, typically including sensitive and resistant staphylococci, streptococci, and enterococci. Empiric antibiotic regimens should reflect local patterns of infection and antibiotic resistance; however, typical examples of broad-spectrum antibiotic coverage may include

- Native valves: Vancomycin 15 to 20 mg/kg IV every 8 to 12 hours (not to exceed 2 g per dose)
- Prosthetic valve: Vancomycin 15 to 20 mg/kg IV every 8 to 12 hours (not to exceed 2 g per dose) plus gentamicin 1 mg/kg IV every 8 hours plus either cefepime 2 g IV every 8 hours or imipenem 1 g IV every 6 to 8 hours (maximum dose 4 g per day)

As soon as possible, the empiric drug regimen should be adjusted based on culture results

IV drug abusers frequently do not adhere to treatment, abuse IV access lines, and tend to leave the hospital too soon. For such patients, short-course IV or (less preferably) oral therapy may be used. For right-sided endocarditis caused by methicillin-sensitive *S. aureus*, nafcillin 2 g IV every 4 hours plus gentamicin 1 mg/kg IV every 8 hours for 2 weeks is effective, as is a 4-week oral regimen of ciprofloxacin 750 mg twice a day plus rifampin 300 mg twice a day. Left-sided endocarditis does not respond to 2-week courses.

Cardiac valve surgery. Surgery (debridement, valve repair, or valve replacement) is sometimes required for treatment of infectious endocarditis. Surgery is typically indicated in

- Patients with heart failure (particularly those with prosthetic, aortic or mitral native valve endocarditis, and those with pulmonary edema or cardiogenic shock)
- Patients with uncontrolled infection (those with persistent infection, infection with fungal or resistant organisms, recurrent prosthetic valve endocarditis, or endocarditis complicated by heart block, abscess, aneurysm, fistula, or enlarging vegetation)
- Patients at risk for embolism (particularly those with prosthetic, aortic or mitral native valve endocarditis, and large vegetations [defined in the United States as > 10 mm] or those with recurrent emboli)

Timing of surgery requires experienced clinical judgment. If heart failure caused by a correctable lesion is worsening (particularly when the organism is *S. aureus*, a gram-negative bacillus, or a fungus), surgery may be required after only 24 to 72 hours of antimicrobial therapy.

In patients with **prosthetic valves,** surgery may be required when

- Transesophageal echocardiography shows valve dehiscence on a paravalvular abscess
- Valve dysfunction precipitates heart failure
- Recurrent emboli are detected
- Infection is caused by an antimicrobial-resistant organism

Right-sided endocarditis is usually managed medically. If surgery is necessary (due to heart failure or lack of therapeutic response), then valve repair is preferred over

replacement to avoid future prosthetic valve infection due to any continued IV drug use.
Surgery is usually delayed for a month after intracranial hemorrhage or major ischemic stroke.

General material and educational and methodological support of the lecture:
- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:
1) Definition of infective endocarditis.
2) Etiology factors for infective endocarditis.
3) Pathogenesis of infective endocarditis.
4) Classification of infective endocarditis.
5) Symptoms of infective endocarditis.
6) Diagnosis of infective endocarditis.
7) Treatment of infective endocarditis.
8) Prognosis for infective endocarditis.

List of used sources:
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Lecture № 8

Topic: Pericarditis

Actuality of theme: Pericardial diseases can present clinically as acute pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis. Patients can subsequently develop chronic or recurrent pericarditis. Structural abnormalities including congenitally absent pericardium and pericardial cysts are usually asymptomatic and are uncommon. Clinicians are often faced with several diagnostic and management questions relating to the various pericardial syndromes: What are the diagnostic criteria for the vast array of pericardial diseases? Which diagnostic tools should be used? Who requires hospitalization and who can be treated as an outpatient? Which medical management strategies have the best evidence base? When should corticosteroids be used? When should surgical pericardiectomy be considered?

Goal: explain the essence of the pericarditis, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention

Key words: pericardium, exudative pericarditis, dry pericarditis, constrictive pericarditis, ECG, echocardiography

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease i. Treatment j. Prevention	 II II II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

III	The final stage		References, questions, tasks	10% (10 min)
4.	Lecture summary, general conclusions	III		
5.	Answers to possible questions	III		
6.	Tasks for self-training	III		

Content of the lecture

Terminology and classification

Pericarditis is an inflammation of the pericardial sac, a fibroelastic structure that usually contains
15-50 ml of plasma ultrafiltrate.

A congenitally absent pericardium or pericardial cysts are uncommon structural abnormalities that are usually asymptomatic whereas
pericardial effusion,
cardiac tamponade,
constrictive pericarditis and
acute pericarditis are forms of pericardial disease that are symptomatic.
Moreover, patients affected by pericarditis can subsequently develop chronic or recurrent pericarditis, which is difficult to prevent.

Less common causes

- Autoimmune reaction
- Trauma
- Neoplasm
- Idiopathic
- Bacterialinfection
- TB
- Rheumatic fever
- HIV – these patient may get staphylococcal pericarditis – which is often fatal

Classification of Pericarditis

1. Acute pericarditis (<6 weeks)
   a. Effusive
   b. Fibrinous
2. Subacute pericarditis (>6 weeks to 6 months)
3. Chronic pericarditis (>6 months)
   a. Effusive
   b. Adhesive
   c. Effusive-adhesive
   d. Constrictive

Etiology and pathogenesis of pericarditis

The outer layer of the heart is made of fibrous tissue which does not easily stretch, so once fluid begins to enter the pericardial space, pressure starts to increase. If fluid continues to accumulate, each successive diastolic period leads to less blood entering the

ventricles. Eventually, increasing pressure on the heart forces the septum to bend in towards the left ventricle, leading to a decrease in stroke volume. This causes the development of obstructive shock, which if left untreated may lead to cardiac arrest (often presenting as pulseless electrical activity).

Clinical picture of pericarditis

Sharp pain – this can vary in site and severity, however is usually retrosternal. It often radiates to the shoulders and neck, and is aggravated by deep breathing (pleuritic), movement, change of position, exercise and swallowing.

- The pain is typically relieved by leaning forwards
- The differentials for this type of pain are basically pleurisy and pericarditis

Fever – a low grade fever may be present

Pericardial effusion – this is present whatever the cause. However, it can be a result of different factors (depending on the cause); e.g. serous, purulent, haemorrhagic, fibrinous

- Fibrinous exudates – can eventually lead to adhesion
- Serous – this produces a large amount of straw-coloured fluid, with a very high protein content • Haemorrhagic – usually due to malignant disease, most commonly carcinoma of the breast, bronchus, and lymphoma.
- Purulent – this is rare, and may be a complication of septicaemia.
- Pericardial effusion may press on the surrounding tissues, particularly the bronchi, resulting in dyspnoea Pericardial friction rub – this is a high pitched superficial scratching or crunching sound, that is produced by movement of the pericardium. It is diagnostic for pericarditis. Usually heard in systole but may also be heard in diastole.
- It is classically heard in three, or two ('to and fro' rub) phases – i.e. this means it is heard 3 times or twice during one cardiac cycle
- The rubs are typically heard best with the diaphragm at the left lower sternal edge at full expiration

Laboratory data in pericarditis

ECG – this will show widespread saddle shaped ST elevation. There may also be PR interval depression – and if both of these are present it is pretty much diagnostic for pericarditis

- Later there may also be T wave inversion – especially if myocarditis is also present. This will eventually resolve
- The ST elevation is often distributed in both inferior and anterior leads – thus this helps to distinguish it from MI

FBC – there may be leukocytosis or lymphocytosis due to viral or bacterial infection

CXR, echo, radionucleotide scans – these are all of little use in uncomplicated disease

Treatment of pericarditis (program)

Pre-hospital care Initial treatment given will usually be supportive in nature, for example administration of oxygen, and monitoring. There is little care that can be provided pre-hospital other than general treatment for shock.

Some teams have performed an emergency thoracotomy to release clotting in the pericardium caused by a penetrating chest injury. Prompt diagnosis and treatment is the key to survival with tamponade.

Some pre-hospital providers will have facilities to provide pericardiocentesis, which can be life-saving. If the patient has already suffered a cardiac arrest, pericardiocentesis alone cannot ensure survival, and so rapid evacuation to a hospital is usually the more appropriate course of action.

Hospital management

Initial management in hospital is by pericardiocentesis. This involves the insertion of a needle through the skin and into the pericardium and aspirating fluid under ultrasound guidance preferably. This can be done laterally through the intercostal spaces, usually the fifth, or as a subxiphoid approach.

A left parasternal approach begins 3 to 5 cm left of the sternum to avoid the left internal mammary artery, in the 5th intercostal space. Often, a cannula is left in place during resuscitation following initial drainage so that the procedure can be performed again if the need arises. If facilities are available, an emergency pericardial window may be performed instead, during which the pericardium is cut open to allow fluid to drain.

Following stabilization of the patient, surgery is provided to seal the source of the bleed and mend the pericardium. In people following heart surgery the nurses monitor the amount of chest tube drainage.

If the drainage volume drops off, and the blood pressure goes down, this can suggest tamponade due to chest tube clogging.

In that case, the patient is taken back to the operating room for an emergency reoperation. If aggressive treatment is offered immediately and no complications arise (shock, AMI or arrhythmia, heart failure, aneurysm, carditis, embolism, or rupture), or they are dealt with quickly and fully contained, then adequate survival is still a distinct possibility.

- Treat theun derlying cause!
- Bed-rest and oral NSAID's. however – do not use NSAID's in the first few days after MI – as they associated with increased risk of myocardial rupture.
- Corticosteroids may be given as symptomatic relief, but there is no evidence that they increase the speed of cure Complications
- If pericarditis lasts more than 6-12 months, then chronic pericarditis is said to exist. In these cases, it is possible for the pericardium to thicken, and this can restrict ventricular filling, and then restrictive pericarditis is present Pericardial effusion and cardiac tamponade Pericardial effusion – this is collection of fluid within the pericardial sac. It most commonly occurs with pericarditis. When the pericardial sac fills, this puts pressure on the ventricles, and compromises their pumping function. This causes problems with circulation. When this occurs, it is known as cardiac tamponade. Tamponade generally comes on very quickly – it is acute heart failure due to compression.

Clinical features

- Heart sounds soft anddistant
- Apex beatis comm only obscured
- Friction rub – may be present in the early stages (of pericarditis), but as the amount

of fluid increases, the rub disappears

- Ewart's sign – this is rare – the effusion can compress the base of the left lung producing an area that is dull to percussion, just below the angle of the left scapula.
- Features of tamponade
- Raised JVP, with a sharp rise, and sharp y descent –Freidrich's sign.
- Kussmaul's sign – raised JVP + increased neck vein distension in inspiration
- Pulsus paradoxus – this is an exaggeration of the normal variation of the pulse during inspiration and expiration. Normally the pulse is stronger during inspiration, and weaker during expiration. This becomes exaggerated such that the radial pulse may not be palpable, due to a substantial drop in BP Investigations
- ECG – low voltage QRS complexes
- CXR – will show an enlarged heart (globular or pear shaped), with precise outlines. The pulmon ar yveins will not be distended.
- Echo – this is the most useful test, as it is able to directly detect the tamponade
- MRI – maybe do one of these if you suspect haemopericardium
- Pericardiocentesis – this is indicated when you suspect an infection is the cause (e.g. TB, malignancy)
- Pericardial biopsy – this can be done if you still suspect TB, despite a negative pericardiocentesis
- Blood cultures / antibody screen – to look for the underlying cause Treatment Treat the underlying cause – most pericardial effusions resolve spontaneously. In cases of a rapid forming effusion, then tamponade will probably result; and acute treatment would involve pericardiocentesis, and perhaps a drain, just to allow the fluid to escape.
- If it keeps coming back after being drained, then it is most likely the result of malignancy. If this is the case, then you can treat it with fenestration – which is where you create a 'window' in the pericardium, which allows the fluid to drain into the surrounding tissue Constrictive pericarditis This can be a result of TB and other infectious causes. The pericardium may become hard, fibrous and calcified. It also occurs after open heart surgery. Most of the time it is asymptomatic, but if it starts to interfere with ventricular filling, then we say constrictive pericarditis is present.
- Generally, the changes occur over a long period of time, and thus other mechanisms have time to compensate. Thus it is not as dangerous as tamponade. The signs and investigations are very similar to that of pericardial effusion. However, there may be other more chronic signs also, such as:
- Pulmonary effusion – dyspnoea, cough, orthopnoea
- Reduced cardiac output – hypotension, fatigue, reflex tachycardia
- Pulmonary venous congestion – ascites, hepatomegaly, raised JVP
- Atrial dilation – which in 30% of patients will cause atrial fibrillation
- Constrictive pericarditis is very difficult to distinguish from restrictive cardiomyopathy. The final diagnosis may depend on complex Doppler flow studies. Treatment This involves complete resection of the pericardium.

This is dangerous, and has a high rate of complications. the earlier in the progression of the disease that the resection is performed, the greater the chance of success. If TB

is also present, then the calcified pericardium suggests chronic disease.

General material and educational and methodological support of the lecture:
- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:

1. Define pericarditis?
2. Define of pericardial effusion?
3. Give classification of pericarditis ?
4. Give a list of etiological factors of pericarditis ?
5. Describe the main pathogenetic mechanisms of pericarditis ?
6. Identify the main clinical syndromes pericarditis?
7. Determination of clinical features of pericarditis?
8. Give a list of laboratory diagnostic criteria for pericarditis?
9. Define a treatment program for pericarditis?
10. Describe prevention measures and determine the forecast for pericarditis?

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Lecture № 9

Topic: Rhythm and conduction disorders

Actuality of theme: The normal heart beats in a regular, coordinated way because electrical impulses generated and spread by myocytes with unique electrical properties trigger a sequence of organized myocardial contractions. Arrhythmias and conduction disorders are caused by abnormalities in the generation or conduction of these electrical impulses or both.

Any heart disorder, including congenital abnormalities of structure (eg, accessory atrioventricular connection) or function (eg, hereditary ion channelopathies), can disturb rhythm. Systemic factors that can cause or contribute to a rhythm disturbance include electrolyte abnormalities (particularly low potassium or magnesium), hypoxia, hormonal imbalances (eg, hypothyroidism, hyperthyroidism), and drugs and toxins (eg, alcohol, caffeine).

Goal: explain the essence of the rhythm and conduction disorders process, causes, role in the etiopathogenesis of various factors, approaches to diagnosis, treatment and prevention.

Key words: tachycardia, bradycardia, sinus arrhythmia, supraventricular arrhythmia, ventricular arrhythmia, SA block, AV block, left bundle brunch block, right bundle brunch block

Plan and structure of the lecture:

№	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution
I 1. 2.	Preparatory stage Setting a learning goal Providing positive motivation	 I I	In accordance with the publication "Guidelines for planning, preparation and analysis of lectures"	5% (5 min)
II 3.	The main stage Teaching lecture material according to the plan: a. Relevance of the topic b. Definition c. Classification d. Etiology and main links of pathogenesis e. Symptoms and signs f. Diagnostic criteria g. Main syndromes and differential diagnosis h. Criteria for the severity of disease	 II II II II II II II II	Slide presentation of lecture material Extracts from medical histories of patients. Excerpts from clinical guidelines for the provision of medical care to patients.	85% (75 min)

	i. Treatment j. Prevention	II II		
III 4. 5. 6.	The final stage Lecture summary, general conclusions Answers to possible questions Tasks for self-training	 III III III	References, questions, tasks	10% (10 min)

Content of the lecture

DISORDERS OF RHYTHM

The heart beat is normally initiated by an electrical discharge from the sinoatrial (sinus) node.

The atria and ventricles then depolarise sequentially as electrical depolarisation passes through specialised conducting tissues .

The sinus node acts as a pacemaker and its intrinsic rate is regulated by the autonomic nervous system; vagal activity decreases the heart rate, and sympathetic activity increases it via cardiac sympathetic nerves and circulating catecholamines If the sinus rate becomes unduly slow, another, more distal part of the conducting system may assume the role of pacemaker.

This is known as an escape rhythm and may arise in the atrioventricular (AV) node or His bundle (junctional rhythm) or the ventricles (idioventricular rhythm).

A cardiac arrhythmia is a disturbance of the electrical rhythm of the heart. Arrhythmias are often a manifestation of structural heart disease but may also occur because of abnormal conduction or depolarisation in an otherwise healthy heart.

A heart rate of more than 100/min is called a tachycardia, and a heart rate of less than 60/min is called a bradycardia.

There are three main mechanisms of tachycardia:

• Increased automaticity. The tachycardia is produced by repeated spontaneous depolarisation of an ectopic focus, often in response to catecholamines.

• Re-entry. The tachycardia is initiated by an ectopic beat and sustained by a re-entry circuit

Most tachyarrhythmias are due to re-entry.

• Triggered activity. This can cause ventricular arrhythmias in patients with coronary artery disease. It is a form of secondary depolarisation arising from an incompletely repolarised cell membrane. Bradycardia may be due to:

• Reduced automaticity, e.g. sinus bradycardia.

• Blocked or abnormally slow conduction, e.g. AV block.

Sinoatrial nodal rhythms

Sinus arrhythmia Phasic alteration of the heart rate during respiration (the sinus rate increases during inspiration and slows during expiration) is a consequence of normal parasympathetic nervous system activity and can be pronounced in children. Absence of this normal variation in heart rate with breathing or with changes in posture may be a feature of autonomic neuropathy

Sinus bradycardia sinus rate of less than 60/min may occur in healthy people at rest and is a common finding in athletes. Asymptomatic sinus bradycardia requires no treatment. Symptomatic acute sinus bradycardia usually responds to intravenous atropine 0.6–1.2 mg. Patients with recurrent or persistent symptomatic sinus bradycardia should be considered for pacemaker implantation.
Sinus tachycardia This is defined as a sinus rate of more than 100/min, and is usually due to an increase in sympathetic activity associated with exercise, emotion, pregnancy or pathology Young adults can produce a rapid sinus rate, up to 200/min, during intense exercise

Sinoatrial disease (sick sinus syndrome) Sinoatrial disease can occur at any age but is most common in older people. The underlying pathology involves fibrosis, degenerative changes or ischemia of the SA (sinus) node. The condition is characterized by a variety of arrhythmias and may present with palpitation, dizzy spells or syncope, due to intermittent tachycardia, bradycardia, or pauses with no atrial or ventricular activity (SA block or sinus arrest)

Atrial tachyarrhythmias
Atrial ectopic beats (extrasystoles, premature beats) These usually cause no symptoms but can give the sensation of a missed beat or an abnormally strong beat. The ECG shows a premature but otherwise normal QRS complex; if visible, the preceding P wave has a different morphology because the atria activate from an abnormal site. In most cases, these are of noconsequence, although very frequent atrial ectopic beats may herald the onset of atrial fibrillation. Treatment is rarely necessary but β-blockers can be used if symptoms are intrusive

Atrial tachycardia may be a manifestation of increased atrial automaticity, sinoatrial disease or digoxin toxicity. It produces a narrow-complex tachycardia with abnormal P-wave morphology, sometimes associated with AV block if the atrial rate is rapid. It may respond toβ-blockers, which reduce automaticity, or class I or III anti-arrhythmic drugs The ventricular response in rapid atrial tachycardias may be controlled by AV node-blocking drugs. Catheter ablation can be used to target the ectopic site and should be offered as an alternative to anti-arrhythmic drugs in patients with recurrent atrial tachycardia.

Atrial flutter is characterized by a large (macro) re-entry circuit, usually within the right atrium encircling the tricuspid annulus. The atrial rate is approximately300/min, and is usually associated with 2 : 1, 3 : 1 or 4 : 1AV block (with corresponding heart rates of 150, 100 or 75/min). Rarely, in young patients, every beat is conducted, producing a rate of 300/min and, potentially, haemodynamic compromise.

The ECG shows saw toothed flutter waves When there is regular 2 : 1 AV block, it may be difficult to identify flutter waves that are buried in QRS complexes and T waves.
Atrial flutter should always be suspected when there is a narrow-complex tachycardia

of 150/min. Carotid sinus pressure or intravenous adenosine may help to establish the diagnosis by temporarily increasing the degree of AV block and revealing flutter.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an overall prevalence of 0.5%in the adult population of the UK. The prevalence rises with age, affecting 1% of those aged 60–64 years, increasing to 9% of those aged over 80 years. AF is a complex arrhythmia characterized by both abnormal automaticfiring and the presence of multiple interacting re-entry circuits looping around the atria.

Episodes of atrial fibrillation are initiated by rapid bursts of ectopic beats arising from conducting tissue in the pulmonary veins or from diseased atrial tissue. AF becomes sustained because of re-entrant conduction within the atria or sometimes because of continuous ectopic firing Re-entry is more likely to occur in atria that are enlarged, or in which conduction is slow (as is the case in many forms of heart disease). During episodes of AF, the atria beat rapidly but in an uncoordinated and ineffective manner. The ventricles are activated irregularly at a rate determined by conduction through the AV node. This produces the characteristic 'irregularly irregular' pulse. The ECG shows normal but irregular QRS complexes; there are no P waves but the baseline may show irregular fibrillation waves

Treatment of rhythm disorders

Rhythm control. An attempt to restore sinus rhythm is particularly appropriate if the arrhythmia causes troublesome symptoms and if there is a modifiable or treatable underlying cause. Electrical cardioversion is initially successful in three-quarters of patients but relapse is frequent (25–50% at 1 month and 70–90% at1 year). Attempts to restore and maintain sinus rhythm are most successful if AF has been present for less than3 months, the patient is young and there is no important structural heart disease. Immediate cardioversion, after administration of intravenous heparin, is appropriate if AF has been present for under 48 hours. In stable patients with no history of structural heart disease, intravenous flecainide (2 mg/kg over 30 mins, maximum dose 150 mg) canbe used for pharmacological cardioversion and willrestore sinus rhythm in 75% of patients within 8 hours. In patients with structural or ischemic heart disease, intravenous amiodarone can be given via a central venous catheter. Electrical cardioversion, using a DC shock, is an alternative and is often effective when drugs fail. In other situations, DC cardioversion should be deferred until the patient has been established on warfarin, with an international normalized ratio (INR) of more than 2.0 for a minimum of 4 weeks, and any underlying problems, such as hypertension or alcohol excess, have been eliminated.

Anticoagulation should be maintained for at least 3 months following successful cardioversion. If AF recurs, further cardioversion may be appropriate but consideration should be given to pretreatment with amiodarone to reduce the risk of recurrence. Catheter ablation is sometimes used to help restore and maintain sinus rhythm in resistant cases, but is a less effective treatment than for paroxysmal AF.

Rate control. If sinus rhythm cannot be restored, treatment should be directed at maintaining an appropriate heart rate. Digoxin, β-blockers and rate-limiting calcium antagonists, such as verapamil or diltiazem, reduce the ventricular rate by increasing the degree of AV block. This alone may produce a striking improvement in cardiac function, particularly in patients with mitral stenosis. Beta-blockers and rate-limiting calcium antagonists are more effective than digoxin at controlling the heart rate during exercise and have additional benefits in patients with hypertension or structural heart disease. Combination therapy (e.g. digoxin and atenolol) is often advisable but rate-limiting calcium channel antagonists should not be used with β-blockers because of the risk of bradycardia. In exceptional cases, poorly controlled and symptomatic AF can be treated by deliberately inducing complete AV nodal block with catheter ablation; a permanent pacemaker must be implanted beforehand. This is known as the 'pace and ablate' strategy.

Prevention of thromboembolism Loss of atrial contraction and left atrial dilatation cause stasis of blood in the LA and may lead to thrombus formation in the left atrial appendage. This predisposes patients to stroke and other forms of systemic embolism. The annual risk of stroke in patients with AF is influenced by many factors, and in each patient a decision has to be made about the risk of stroke versus the risk of anticoagulation. Several large randomized trials have shown that treatment with adjusted-dose warfarin (target INR 2.0–3.0) reduces the risk of stroke by about two-thirds, at the cost of an annual risk of bleeding of 1– 1.5%, whereas treatment with aspirin reduces the risk of stroke by only one-fifth, is associated with significant bleeding risk and, although still included in European guidelines, has a very limited role. Warfarin is thus indicated for patients with AF who have specific risk factors for stroke. In intermittent AF, the risk of stroke is only loosely related to the frequency and duration of AF episodes, so stroke prevention guidelines do not distinguish between those with paroxysmal, persistent and permanent AF. An assessment of the risk of embolism helps to define the possible benefits of antithrombotic therapy, which must be balanced against its potential hazards. Risk stratification is based on clinical factors using the CHA2DS2-VASC scoring system. Echocardiographic assessment (e.g. left atrial size) is of limited value in predicting stroke risk and is mainly used to identify associated structural disease. Oral anticoagulation is indicated in patients at moderate or high risk of stroke, unless there is an unacceptable bleeding risk. The choice of oral anticoagulant is widening

'Supraventricular' tachycardias The term 'supraventricular tachycardia' (SVT) is commonly used to describe regular tachycardias that have a similar appearance on ECG. These are usually associated with a narrow QRS complex and are characterized by are-entry circuit or automatic focus involving the atria. The term SVT is misleading, as, in many cases, the ventricles also form part of the re-entry circuit, such as inpatients with AV re-entrant tachycardia. Atrioventricular nodal re-entrant tachycardia

Atrioventricular nodal re-entrant tachycardia (AVNRT)is due to re-entry in a circuit involving the AV node and its two right atrial input pathways: a superior 'fast' pathway and an inferior 'slow' pathway This produces a regular tachycardia with a rate of 120–240/min. It tends to occur in the absence of structural heart disease and episodes may last from a few seconds to many hours. The patient is usually aware of a rapid, very forceful, regular heart beat and may experience chest discomfort, lightheadedness or breathlessness. Polyuria, mainly due to the release of atrial natriuretic peptide, is sometimes a feature. The ECG usually shows a tachycardia with normal QRS complexes but occasionally there may be ratedependent bundle branch block.

Management

Treatment is not always necessary. However, an episode may be terminated by carotid sinus pressure or by the Valsalvamanoeuvre. Adenosine (3–12 mg rapidly IV in incremental doses until tachycardia stops) or verapamil(5 mg IV over 1 min) will restore sinus rhythm in most cases. Intravenous β-blocker or flecainide can also be used. In rare cases, when there is severe haemodynamiccompromise, the tachycardia should be terminated byDC cardioversion). In patients with recurrent SVT, catheter ablationis the most effective therapy and will permanentlyprevent SVT in more than 90% of cases. Alternatively,prophylaxis with oral β-blocker, verapamil orflecainide may be used but commits predominantlyyoung patients to long-term drug therapy and cancreate difficulty in female patients, as these drugs arenormally avoided during pregnancy

Ventricular tachyarrhythmias

Ventricular ectopic beats (extrasystoles, premature beats) QRS complexes in sinus rhythm are normally narrow because the ventricles are activated rapidly and simultaneously via the His–Purkinje system. The complexes of ventricular ectopic beats (VEBs) are premature, broad and bizarre because the ventricles are activated sequentially rather than simultaneously. The complexes may be unifocal (identical beats arising from a single ectopic focus) or multifocal (varying morphology with multiple foci, 'Couplet' and 'triplet' are the terms used to describe two or three successive ectopic beats. A runof alternating sinus and ventricular ectopic beats is known as ventricular 'bigeminy'.

Ectopic beats produce a low stroke volume because left ventricular contraction occurs before filling is complete. The pulse is therefore irregular, with weak or missed beats .Patients are usually asymptomatic but may complain of an irregular heart beat, missed beats or abnormally strong beats (due to the increased output of the postectopicsinus beat). The significance of VEBs depends on the presence or absence of underlying heart disease. Ventricular ectopic beats in otherwise healthy subjects VEBs are frequently found in healthy people and their prevalence increases with age. Ectopic beats in patients with otherwise normal hearts are more prominent at rest and disappear with exercise.

Treatment is not necessary, unless the patient is highly symptomatic, in which case β-blockers or, in some situations, catheter ablation can be used. VEBs are sometimes a manifestation of otherwise subclinical heart disease, such as coronary artery disease

or cardiomyopathy. There is no evidence that anti-arrhythmic therapy improves prognosis but the discovery of very frequent VEBs should prompt investigations, such as an echocardiogram (looking for structural heart disease) and an exercise stress test (to detect underlying ischemic heart disease).

Ventricular ectopic beats associated with heart disease Frequent VEBs often occur during acute MI but need no treatment. Persistent, frequent (over 10/hr) VEBs in patients who have survived the acute phase of MI indicate a poorer long-term outcome. Other than β-blockers, anti-arrhythmic drugs do not improve and may even worsen prognosis. VEBs are common in patients with heart failure of any cause, including cardiomyopathy. While they are associated with an adverse prognosis, this is not improved by anti-arrhythmic drugs. Effective treatment of the heart failure may suppress the ectopic beats. VEBs are also a feature of digoxin toxicity, and mayoccur as 'escape beats' in patients with bradycardia. Treatment is that of the underlying condition.

Ventricular tachycardia

Ventricular tachycardia (VT) occurs most commonly in the settings of acute MI, chronic coronary artery disease, and cardiomyopathy. It occurs when there is extensive ventricular disease, such as impaired left ventricular function or a left ventricular aneurysm. In these settings, VT may cause hemodynamic compromise or degenerate into ventricular fibrillation. It is caused by abnormal automaticity or triggered activity in ischemic tissue, or by re-entry within scarred ventricular tissue.

Patients may complain of palpitation or symptoms of low cardiac output, e.g. dizziness, dyspnea or syncope. The ECG shows tachycardia and broad, abnormal QRS complexes with a rate of more than 120/min VT may be difficult to distinguish from SVT with bundle branch block or pre-excitation (WPW syndrome). Features in favor of a diagnosis of VT are listed in A 12-lead ECG or electrophysiology study may help establish the diagnosis.

Management

Prompt action to restore sinus rhythm is required and should usually be followed by prophylactic therapy. Synchronised DC cardioversion is the treatment of choice if systolic BP is less than 90 mmHg. If the arrhythmias well tolerated, intravenous amiodarone maybe given as a bolus, followed by a continuous infusion. Intravenous lidocaine can be used but may depress left ventricular function, causing hypotension or acute heart failure. Hypokalaemia, hypomagnesaemia, acidosis and hypoxemia should be corrected. Beta-blockers are effective at preventing VT by reducing ventricular automaticity. Amiodarone can be added if additional control is needed. Class Ic anti-arrhythmicdrugs should not be used for prevention of VT in patients with coronary artery disease or heart failure because they depress myocardial function and can be proarrhythmic (increase the likelihood of a dangerous arrhythmia). In patients at high risk of arrhythmic death(e.g. those with poor left ventricular function, or where VT is associated with hemodynamic compromise), theuse of an implantable cardiac defibrillator is recommended. Rarely, surgery (e.g. aneurysm resection)or

catheter ablation can be used to interrupt the arrhythmia focus or circuit in patients with VT associated with a myocardial infarct scar.

Atrio-ventricular and bund lebranch block

Atrioventricular block

Atrioventricular conduction is influenced by autonomic activity. AV block can therefore be intermittent and only evident when the conducting tissue is stressed by a rapid atrial rate. Accordingly, atrial tachyarrhythmia are often associated with AV block

First-degree atrioventricular block In this condition, AV conduction is delayed and so the PR interval is prolonged (>0.20 s; Fig. 18.51). It rarely causes symptoms.

Second-degree atrioventricular block In this, dropped beats occur because some impulses from the atria fail to conduct to the ventricles.

Mobitz type I second-degree AV block there is progressive lengthening of successive PR intervals, culminating in a dropped beat. The cycle then repeats itself. This is known as the Wenckebach phenomenon and is usually due to impaired conduction inthe AV node itself. The phenomenon may be physiological and is sometimes observed at rest or during sleep in athletic young adults with high vagal tone.

In **Mobitz type II** second-degree AV block ,the PR interval of the conducted impulses remains constant but some P waves are not conducted. This is usually caused by disease of the His– Purkinje system and carries a risk of asystole. In 2 : 1 AV block alternate P waves are conducted, so it is impossible to distinguish between Mobitz type I and type II block

Third-degree (complete) atrioventricular block When AV conduction fails completely, the atria and ventricles beat independently .Ventricular activity is maintained by an escape rhythm arising in the AV node or bundle of His (narrow QRS complexes) or the distal Purkinje tissues (broad QRS complexes). Distal escape rhythms tend to be slower and less reliable.

Etiology of complete AV block Congenital Acquired

• Idiopathic fibrosis

• MI/ischemia

• Inflammation Acute (e.g. aortic root abscess in infective endocarditis) Chronic (e.g. sarcoidosis; Chagas' disease)

• Trauma (e.g. cardiac surgery)

• Drugs (e.g. digoxin, β-blocker) Complete AV block produces a slow(25–50/min), regular pulse that, except in the case of congenital complete AV block, does not vary with exercise. There is usually a compensatory increase in stroke volume, producing a large-volume pulse. Cannon waves may be visible in the neck and the intensity of the first heart sound varies due to the loss of AV synchrony.

Stokes–Adams attacks Episodes of ventricular asystole may complicate complete heart block or Mobitz type II second degree AV block, or occur in patients with sinoatrial disease. This may cause recurrent syncope or 'Stokes–Adams' attacks. A typical episode is characterized by sudden loss of consciousness that occurs without warning and results in collapse.

A brief anoxic seizure (due to cerebral ischemia) may occur if there is prolonged

asystole. There is pallor and a death-like appearance during the attack, but when the heart starts beating again, there is a characteristic flush. Unlike in epilepsy, recovery is rapid. Sinoatrial disease and neurocardiogenic syncope may cause similar symptoms.

Management

Atrioventricular block complicating acute myocardial infarction Acute inferior MI is often complicated by transient AV block because the right coronary artery (RCA) supplies the AV node.

There is usually a reliable escape rhythm and, if the patient remains well, no treatment is required.

Symptomatic second- or third-degree AV block may respond to atropine (0.6 mg IV, repeated as necessary)or, if this fails, a temporary pacemaker. In most cases, the AV block will resolve within 7–10 days. Second- or third-degree AV heart block complicating acute anterior MI indicates extensive ventricular damage involving both bundle branches and carries a poor prognosis.

Asystole may ensue and a temporary pacemaker should be inserted promptly. If the patient presents with asystole, IV atropine (3 mg) or IV isoprenaline (2 mg in 500 mL 5% dextrose, infused at 10–60 mL/hr) may help to maintain the circulation until a temporary pacing electrode can be inserted. External (transcutaneous)pacing can provide effective temporary rhythm support.

Chronic atrioventricular block Patients with symptomatic bradyarrhythmias associated with AV block should receive a permanent pacemaker(see below). Asymptomatic first-degree or Mobitz typeI second-degree AV block (Wenckebach phenomenon)does not require treatment but may be an indication of serious underlying heart disease. A permanent pacemaker is usually indicated in patients with asymptomatic Mobitz type II second- or third-degree AV heart block because of the risk of asystole and sudden death. Pacing improves prognosis.

Bundle branch block and hemiblock

Conduction block in the right or left bundle branch can occur as a result of many pathologies, including ischemic or hypertensive heart disease or cardiomyopathies Common causes of bundle branch block

Right bundle branch block

- Normal variant
- Right ventricular hypertrophy or strain, e.g. pulmonary embolism
- Congenital heart disease, e.g. atrial septal defect
- Coronary artery disease Left bundle branch block
- Coronary artery disease
- Hypertension
- Aortic valve disease
- Cardiomyopathy

The left bundle branch divides into an anterior and a posterior fascicle. Damage to the conducting tissue at this point (hemiblock) does not broaden the QRS complex but alters the mean direction of ventricular depolarization (mean QRS axis), causing left axis deviation in left anterior hemiblock and right axis deviation in left posterior hemiblock The combination of right bundle branch block and left anterior or posterior hemiblock is known as bifascicular block.

Wolff–Parkinson–White syndrome and atrioventricular re-entrant tachycardia
Here, an abnormal band of conducting tissue connects the atria and ventricles. This 'accessory pathway' comprises rapidly conducting fibres which resemble Purkinje tissue, in that they conduct very rapidly and are rich in sodium channels. In around half of cases, this pathway only conducts in the retrograde direction (from ventricles to atria) and thus does not alter the appearance of the ECG in sinus rhythm. This is known as a concealed accessory pathway. In the rest, the pathway also conducts antegradely (from atria to ventricles) so AV conduction in sinus rhythm is mediated via both the AV node and the accessory pathway, distorting the QRS
ECG during this tachycardia is almost indistinguishable from that of AVNRT Carotid sinus pressure or intravenous adenosine can terminate the tachycardia. If atrial fibrillation occurs, it may produce a dangerously rapid ventricular rate because the accessory pathway lacks the rate-limiting properties of the AV node

Anti-arrhythmic drug therapy
Classification
Anti-arrhythmic drugs may be classified according totheir mode or site of action
Classification of anti-arrhythmic drugs by effect on the intracellular action potential
Class I: membrane-stabilising agents (sodium channel blockers) (a) Block Na+ channel and prolong action potential • Quinidine, disopyramide (b) Block Na+ channel and shorten action potential
• Lidocaine, mexiletine (c) Block Na+ channel with no effect on action potential • Flecainide, propafenone
Class II: β-adrenoceptor antagonists (β-blockers) • Atenolol, bisoprolol, metoprolol
Class III: drugs whose main effect is to prolong the action potential • Amiodarone, dronedarone, sotalol Class IV: slow calcium channel blockers
• Verapamil, diltiazem N.B. Some drugs (e.g. digoxin, ivabradine and adenosine) have no place in this classification, while others have properties in more than one class: e.g. amiodarone, which has actions in all four classes.

Anti-arrhythmic drugs: principles of use
Anti-arrhythmic drugs are potentially toxic and should be used carefully according to the following principles:
• Many arrhythmias are benign and do not require specific treatment
• Precipitating or causal factors should be corrected if possible, e.g. excess alcohol or caffeine consumption, myocardial ischaemia, hyperthyroidism, acidosis, hypokalaemia and hypomagnesaemia
• If drug therapy is required, it is best to use as few drugs as possible

• In difficult cases, programmed electrical stimulation (electrophysiological study) may help to identify the optimum therapy
• When managing life-threatening arrhythmias, it is essential to ensure that prophylactic treatment is effective. Ambulatory monitoring and exercise testing may be of value
• Patients on long-term anti-arrhythmic drugs should be reviewed regularly and attempts made to withdraw therapy if the factors which precipitated the arrhythmias are no longer operative
• For patients with recurrent SVT, radiofrequency ablation is often preferable to long-term drug therapy

Therapeutic procedures

External defibrillation and cardioversion The heart can be completely depolarized by passing a sufficiently large electrical current through it from an external source. This will interrupt any arrhythmia and produce a brief period of asystole that is usually followed by the resumption of sinus rhythm. Defibrillators deliver a DC, high-energy, short-duration shock via two large electrodes or paddles coated with conducting jelly or a gel pad, positioned over the upper right sternal edge and the apex. Modern units deliver a biphasic shock, during which the shock polarity is reversed mid-shock. This reduces the total shock energy required to depolarize the heart.

Electrical cardioversion This is the termination of an organized rhythm, such as atrial fibrillation or ventricular tachycardia, with a synchronized shock, usually under general anesthesia. The shock is delivered immediately after detection of the Rwave because, if it is applied during ventricular repolarisation (on the T wave), it may provoke ventricular fibrillation. High-energy shocks may cause chest wall pain post-procedure, so, if there is no urgency, it is appropriate to begin with a lower-amplitude shock (e.g. 50 joules), going on to larger shocks if necessary. Patients with atrial fibrillation or flutter of more than 48 hours' duration are at risk of left atrial appendage thrombus, and thus systemic embolism after cardioversion. In such cases, cardioversion should be delayed until effective anticoagulation has been given for at least 4 weeks.

Defibrillation This is the delivery of an unsynchronized shock during a cardiac arrest caused by ventricular fibrillation. The precise timing of the discharge is not important in this situation. In ventricular fibrillation and other emergencies, the energy of the first and second shocks should be 150 joules and thereafter up to 200 joules; there is no need for an anesthetic, as the patient is unconscious.

Catheter ablation Catheter ablation therapy is the treatment of choice for patients with supraventricular tachycardia or atrial flutter, and is a useful treatment for some patients with atrial fibrillation or ventricular arrhythmias

Temporary pacemakers

Temporary pacing involves delivery of an electricalimpulse into the heart to initiate tissue depolarisation and to trigger cardiac contraction. This is achieved by inserting a

bipolar pacing electrode via the internal jugular, subclavian or femoral vein and positioning it at the apex of the RV, using fluoroscopic imaging. The electrode is connected to an external pacemaker with an adjustable energy output and pacing rate. The ECG of right ventricular pacing is characterized by regular broad QRS complexes with a left bundle branch block pattern. Each complex is immediately preceded by a 'pacing spike' Nearly all pulse generators are used in the 'demand' mode, so that the pacemaker will only operate if the heart rate falls below a preset level. Occasionally, temporary atrial or dual-chamber pacing (see below) is used. Temporary pacing may be indicated in the management of transient AV block and other arrhythmias complicating acute MI or cardiac surgery, to maintain the rhythm in other situations of reversible bradycardia (i.e. due to metabolic disturbance or drug overdose), or as a bridge to permanent pacing.

Permanent pacemakers

Permanent pacemakers are small, flat, metal devices that are implanted under the skin, usually in the pectoralarea. They contain a battery, a pulse generator, and programmable electronics that allow adjustment of pacing and memory functions. Pacing electrodes (leads) can be placed via the subclavian or cephalic veins into the RV(usually at the apex), the right atrial appendage or, to maintain AV synchrony, both.

Implantable cardiac defibrillators

In addition to the functions of a permanent pacemaker, implantable cardiac defibrillators (ICDs) can also detect and terminate life-threatening ventricular tachyarrhythmias. ICDs are larger than pacemakers mainly because of the need for a large battery and capacitor to enable cardioversion or defibrillation. ICD leads are similar to pacing leads but have one or two shock coils along the length of the lead, used for delivering defibrillation

Cardiac resynchronisation therapy (CRT)

for heart failure Cardiac resynchronisation therapy (CRT) is a treatment for selected patients with heart failure, in whom cardiac function is further impaired by the presence of left bundle branch block. This conduction defect is associated with left ventricular dys-synchrony (poorly coordinated left ventricular contraction) and can aggravate heart failure in susceptible patients. CRT systems have an additional lead that is placed via the coronary sinus into one of the veins on the epicardial surface of the LV

General material and educational and methodological support of the lecture:

- Working program of the academic discipline
- Syllabus
- Methodical developments for lectures
- Multimedia presentations
- Educational and methodical literature

Questions for self-control:

1. Defining the concept of AV-block ?
2. What are the risk factors for sinus tachycardia?
3. Classification of AV-block ?
4. Classification of AV-block type 2
5. Conduction disorders risk factors?
6.General signs of diagnosis of the CA (ECG, Holter monitoring ECG during the day, a sample with a dosed physical load, transesophageal pacing)?
7. What are the ECG signs of atrial extrasystole?
8. What are the ECG signs of extrasystoles from AV compounds?
9. What are the EGC signs of ventricular extrasystole?
10. Classification of antiarrhythmic drugs, pharmacological recovery of sinus rhythm?

List of used sources:

1. Davidson's "Principles of Practice of Medicine" 20th edition 2018, Elsevier limited.
2. Harrison's "Principles of internal medicine" Volume 1,2, 2018, USA. - Cardiology
3. Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care for atrial fibrillation. Order of the Ministry of Health of Ukraine of June 15, 2018 No. 597.
4. Zoni-Berisso, M; Lercari, F; Carazza, T; Domenicucci, S (2017). "Epidemiology of atrial fibrillation: European perspective."
5. 2020 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter
6. 2020 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death