3.22.1.3 Asymptomatic (silent) ischemia

During the treadmill test in patients with various circulatory disturbances we may uncover patients with ischemic heart disease. Apart from the treadmill test results these patients are usually diagnosed by the use of longitudinal ECG examination with judging the ST segment shape on the ECG. It is a fact that these patients have no symptoms of the ischemic heart disease. Their long lasting monitoring showed that the occurrence of sudden death is common in this group, as well as myocardial infarction or the manifestation of non stable angina pectoris. The progression might be judged only individually. About the prognosis the decisive factors are the left ventricular function, the state of the coronary arteries, the effect of pharmacological therapy, and the possibility of revascularization and even its contraindication

3.23 Acute myocardial infarction

Acute myocardial infarction is a dynamic state, in which a stopped myocardial perfusion leads to myocardial irreversible injury. Acute myocardial infarction **is an anemic necrosis most commonly caused by a closure of a coronary artery** or one of its branches affected by an atherosclerotic process. The causes of the coronary artery closure might be some obvious morphological changes (thrombus based on the atherosclerotic changes), it might also be coronary artery spasm that occurred with or without the presence of the atherosclerotic changes in the affected vessel. The area affected by necrosis can not be changed or drown smaller. It is surrounded by a hypoxic myocardial area of various sizes. In experimental conditions necrosis (death) of the myocytes occur within 15–40 min following the stop of blood flow and a complete coronary artery or its branch occlusion.

The cause of myocardial infarction is most commonly an acute thrombotic closure of the coronary artery affected by atherosclerosis. Sometimes stenosis is not very prominent and the occurrence of myocardial infarction is caused by a rupture of an atherosclerotic plaque or the formation of a thrombus (plug) in this locality. In some cases we are dealing with a coronary spasm (what is known as obstructive form). It is usually compelled with coronary sclerosis. In what is known as the non obstructive form we noticed an increased tone of the large coronary artery, or an increasing tonus of the distal coronary field. An important factor for coronary artery closure is an intimal injury. In the following years it was found out that the endothelium plays a very important role in the coronary artery obstruction. The endothelium modulates the function of the vascular smooth muscle via the liberation of substances that control local constriction and relaxation of the vessels. Haemodynamics factors (increasing the coronary blood flow) and some substances (serotonin, acetylcholin) can activate the liberation of some endothelial relaxing factors - EDRF Endothelium Derived Relaxing Factor. In a normally functioning artery with intact endothelium, the release of EDRF causes vasodilatation. Apart from this it has an antithrombotic effect on the luminal surface of the endothelium. In the presence of the atherosclerotic plaque or an injured endothelium no EDRF is formed or released and so its mentioned functions do not appear. When thrombocytes aggregate on the endothelial surface they will release thromboxan that cause further vasoconstriction and further thrombocyte aggregation. **Endothelial dysfunction** occurs quite often due to some minor insults. It might be an activation of the vascular smooth muscles, that is not so prominent so that to cause a serious arterial occlusion. The endothelial injury is the most probably due to a faster flood flow in the area of the partial functional stenosis. Later on there will be a deposition of thrombocytes on the injured endothelium and a formation of non occlusive micro thrombi. The atherosclerotic process doesn't only lead into a lower translucency of the coronary vessels. During this process a monocellular infiltration, foam cells and leukocytes can release many factors (thromboxan, leukotriens, 5-hydroxytryptamin), these result into thrombocyte aggregation, an increased predisposition for blood coagulation, stimulation of migration and proliferation of other cells. Apart from this they have other affects on the distal segments of the coronary system. The clinically known triggering factors

for myocardial infarction act through disturbing the atherosclerotic plaque (rupture of the plaque) or via increasing the oxygen requirement in patients with a considerable stenosis (see table 3.2).

Factors	**Examples**
Environmental	Smoking, emotional stress, exposure to cold
Associated diseases	Anemia, thyreotoxicosis, hypertension, arrhythmia, infection, polycythemia, fever
Vasoconstricting agents	Amphetamines A
Sudden withdrawal anti angina pharmacotherapy	nitrates, nifedipin, betablockers

Table 3.2: Triggering factors for the occurrence of acute myocardial infarction

The less common causes are:

1. Acute coronary thrombosis without the presence of the atherosclerotic process in the coronary arteries
2. An embolic closure of the coronary artery
3. Coronary artery stenosis that resulted from an inflammatory process in the coronaries (coronaritis)

Myocardial infarction might occur without any atherosclerotic changes in the coronary arteries:

1. Normal coronary arteries:
   - unknown etiology
   - myocardial contusion
   - a state of no equilibrium between the requirement of oxygen and its supply (aortic stenosis, aortic insufficiency, carbon monoxide intoxication, thyreotoxicosis)
2. Embolisation of the coronary arterial system:
   - infective endocarditis
   - left atrial or ventricular thrombosis
   - rheumatic process in the mitral value with atrial fibrillation
   - artificial heart valves
   - cardiopulmonary bypass (thrombocyte aggregation, air)
   - coronary angiography.
3. Non atherosclerotic changes of the coronary arteries:
   - arteritis (Takayasu disease, infective and nonspecific arteritis, polyarteritis nodosa, lupus erythomatosus, and primary chronic polyarteritis
   - Thickening of the coronary artery wall in cases of metabolic diseases or in cases of intimal proliferation (homocystinuria, Fabry's disease, amyloidosis, hyperplasia of the intima coupled with the use of contraceptive steroids or connected with post delivery state, disease of the small coronary arteries (of a diameter 0,1–1,0 mm known as small vessel disease)
   - Narrowing of the coronary artery lumen by other mechanisms (dissection of the coronary artery, spasm of the coronary artery after the withdrawal of nitroglycerine's, a spasm due to a vasoconstriction (Prinzmetal) angina pectoris and normal coronary arteries.
   - Congenital anomalies of the coronary arteries (abnormal origin of the left coronary artery from the pulmonary artery).

The extent of the **coronary spasmus** as an etiological factor is yet not clear. It seems that it can only occasionally be the main primary cause of a sudden cornary artery occlusion. Yet it has a great value as a cofactor. We may induce the coronary spasm experimentally by many substances, for example by the use of ergonovin, acetylcholin, or histamin. It is hence possible to expect that spasm may be not caused by blocking a certain kind of a receptors, but it may occur by affecting a certain mechanism that regulates the vascular contractility. Meantime there

is an intensive study about the effect of endothelin, which is a substance with a prominent vasoconstricting effect. It is 21 amino-peptide, that has the most potent vasoconstrictory action among all the known substances, biological poisons and toxins. It is most probably produced by the vascular wall endothelium. A question whether this substance leads to vasoconstriction directly or it only sensibilities the vasculature for otherwise non effective vasoconstrictory stimuli is not yet solved.

The assume that there will be an irreversible coagulation necrosis of a part of myocardium is through to result from a **critical restriction of perfusion** of a concerned part of cardiac muscle (myocardium) for a relatively long time. In experimental coronary ligature there will be an irreversible myocardial necrosis within 15-40 minutes. The development of necrosis can be influenced in individual cases by many factors, that affect the oxygen supply of the myocardium (the remaining perfusion in case of a heavy coronary stenosis or perfusion by the collateral circulation in case of total obliteration of the coronary artery). The time needed for the necrosis to develop, is affected by the oxygen requirement of the heart (the presence of a morphological factor for e.g.: myocardial hypertrophy, or the presence of some function factors, for e.g.: tachycardia, a high left ventricular wall tension, a high contractility – all these conditions increase the oxygen utilization in the myocardium). The critical time for the development of necrosis can be affected by the combination of the previously mentioned factors.

On the other hand the **thrombotic closure of the coronary arteries** can occur without a necessary following myocardial infarction. Usually in these cases coronary artery stenosis develops very slowly till its final closure. This slow stenotisation will provide adequate time for a network of collateral circulation to develop, and these collaterals will ensure an adequate perfusion of tissues that are supplied by the stenozed artery.

Any stop of the coronary perfusion causes necrosis of the cardiomyocytes over a certain period of time. Individual parts of the myocardium have different sensitivity for hypoxia. The subendocardial area is the most sensitive and the subepicardial area is the most resistant. Even the infarct as a rule is progressing form the subendocardial area to the subepicardial area. **The size of the infarct area is determined** by the following factors:

1. The size of the area nourished by the occluded coronary artery.
2. The period of coronary closure.
3. The oxygen requirement by the myocardium during the coronary occlusion. It was found experimentally that the time period between 10–20 minutes post coronary artery occlusion is very important. If at this time there is a high myocardial requirement for oxygen (for e.g.: due to a present tachycardia), a large infarction will develop. Pharmacologically, for example due to the use of betablockers it is possible to reduce the oxygen need of the myocardium. This protection yet last for only 2–3 hours. If we do not open the occluded coronary artery the resulting infarction will be large as well.
4. The extent of the resting coronary perfusion via the collateral arteries. This is evidently the most important factor that will decide the myocardial sparing. The presence of collaterals is very variable among different individuals. The collateral circulation is important not only for the minimal oxygen supply, but even for the removal of metabolism products, that are an osmotic load on the myocardial cells.
5. Variable ischemia toleration of the myocardium.

It is very important to the development of acute infarction into two phases, the early phase, and the phase of adaptation.

The acute phase of myocardial infarction. From the periodical point of view it includes the first six hours from the developing signs and symptomps of the disease. Its main characteristic lies in that the therapeutical intervention in this period of time has the greatest possibility of achieving a favourable change in the course of the disease.

During the acute phase there are very serious vascular changes in the infarct area. Atheromatous material and mixture of thrombocytes and fibrin can act as **an embolizing material** in the vascular field. The endothelial cells become odematous due to hypoxia. Thrombocytes, leukocytes, and fibrin occlude the small vesseles. As a result of this there will be capillary compression which worsens the function and the effectivness of the collateral circulation. In

this situation the capillary permeability increases till a point where hemorrhage may occur

The phase of cardiac adaptation during the acute myocardial infarction. From the periodical point of view it includes the myocardial events, that take place after the sixth hour of the appearance of signs and symptoms. In this phase the heart (left ventricle) undergoes a geometrical rebuilding of its architecture, what is known as **remodelation**. This process is for more complex than previously thought. We can define two general processes, that lead to changes of the shape (geometry) of the left ventricle after the infarction. The first process is known as expansion of the infarct area and the second is known as the late remodelation of the left ventricle.

Expansion of the infarct area Marks the ventricular dilatation, that occur as a result of an acute stretching, thinning and dilatation of the injured myocardial segment. This process has got a very important role in the development and the final result of the infarction.

It concerns nearly 15 % of acute myocardial infarction cases. And later on, depending on this there might be a permanent dilatation, aneurysm formation (that means a persistent local expansion of the left ventricular wall in the region of the overcomed infarction), rupture of the interventricular septum or the free wall of the left ventricle. Expansion of the myocardium and its rupture often occur in cases of transmural infarcts (known as the Q infarcts, which is a classification that depends upon the electrocardiographical findings, and this corresponds with the hypothesis that we are dealing with a transmural infarction) in patients who have the infarction for the first time and in hypertensive patients.

Many times we use terms like extension of the infarction or reinfarction. These terms do often interchange or one of them is thought to mean the other. They mark a further injury of the left ventricular myocardium. **Extension of the infarct area (expansion of the necrosis)** Is expanded on the base of a new raise of MB isoenzymes of creatinin kinase in the blood (this fact stands for the myocardial necrosis). Extension of the infarct clearly raises the patients mortality. It is quite understood, because it is about an increment in the region of the infarction. Previously an overcomed infarction was increasing the risk of extension.

A delayed remodelation of the left ventricle. Means a gradual ventricular dilatation, that occurs in a healthy myocardium, meaning an area or a segment of the left ventricle not affected by the infarction. It is a process that, from the functional point of view stands for or is compensating the decrease of the left ventricular function which follows the infarction for example, via the Frank-Starling mechanism.

From the pathophysiological point of view it is necessary to explain two important terms:

1. **The myocardial stunning phenomena (stiff myocardium)**. In certain cases a prominent myocardial ischemia can produce a complicated myocardial dysfunction with no proven necrosis. This dysfunction persist for a long time after the equilibrium between the myocardial requirement for oxygen and its actual supply has been established. So despite the renewed establishment of perfusion the functional, ultrastructural, and biochemical abnormalities in the myocardium persist, and this lasts for days or even weeks, for the myocardial function to be fully regenerated.

2. **Phenomena of the hibernating myocardium** (means cold or frozen myocardium). It develops during the chronic reduction of perfusion or in cases of an increase of the oxygen requirements that in turn causes a mild, yet a persistent hypoxia. The myocardium then is down regulated, meaning that it decreases its function to a level which corresponds with its oxygen supply. The remodeling or down regulation stands against the hypothesis that says "the myocardium commits suicide" i.e. necrotizes, and this happens when its supply of blood is reduced for a long time. With this down regulation there will be setting of a new equilibrium, and this will not progress to a state of necrosis. This equilibrium is however very labile and any further worsening in the supply of oxygen or an increase in oxygen requirement will eventually lead into the progression of necrosis. The myocardial segment with dysfunction (e.g. hypokinesis), that have a reduced perfusion but are metabolically active, will eventually loose their dysfunction after a successful reperfusion (renewal of the perfusion in the coronary field) with the help of a surgically created bypass. The evidence about the

presence of induction and control of down regulation of the myocardial function does provide us with some attractive therapeutical approaches for patients with an acute myocardial infarction.

The loss of integrity of a myocardial myocyte in the acute phase of infarction produces a prominent electrophysiological changes, that are usually the cause of arrhythmia.

During the course of an acute myocardial infarction we usually notice the presence of a marked sympathetic nervous system stimulation. This is as well produced by increasing the number of baroreceptors in the ischemic myocardium, and this occurs shortly post the occurrence of the coronary occlusion (as proven in an experiment provided on animals).

The local presence of catecholamins are yet arrhythmogenic, and as they increase the inflow of calcium ions into the cell via the stimulation adenylcyclase. A partial inactivation of the fast Na^+ channels (due to the drop in the membrane potential) leads to a slow conduction of stimuli in the region of infarction. These facts are very important from the arrhythmogenic point of view in the acute myocardial infarction. In this situation there is an increase in the number of the spontaneous ectopic depolarization and a prominent **non homogenity of the electrical characteristics of the myocardium**. This condition occurs inside the infarction area, yet it is mainly in the borderline (being a zone between the non infarction and the ischemic myocardial area). In experiments done on animals we could detect some other metabolic changes, that might have a certain role in the arrhythmogenesis of the acute infarction. This is mainly about these:

- The raise in lactate production shortens the duration of action potential (shortening the refractory period) with a simultaneous drop of the resting membrane potential.
- Phase 4 TAP (the spontaneous depolarization) is usually faster
- Free fatty acids in the presence of hypoxia or ischemia might simultaneously decrease the resting membrane potential and accelerate phase 4. There is a relation between the level of the free fatty acids in the serum of a person suffering from an acute myocardial infarction and the incidence of ventricular disturbances of the cardiac rhythm (see fig. 3.22 on page 204).

Inadequate perfusion (hypoperfusion) of a part of the myocardium leads quickly to its abnormal contraction. Only few seconds after an experimental closure of the coronary artery hypokinesis develop (meaning a drop of the systolic contraction), akinesis (no systolic contraction) or dyskinesis (paradoxical systolic contractions) of that part of the myocardium which lacks the required perfusion. The final results on the general function of the heart as a pump depend on:

1. The size of the area, that is affected by the loss of contractility
2. The functional state of the intact myocardium, being the part, that is not affected by the infarction.

These facts take place mainly in the haemodynamic results of the acute infarction in the human being. From the view of functional status definition of the heart as a pump the following parameters or quantitative changes were defined.

- The reduction of ejection fraction, and the drop of the stroke volume
- The reduction of dp/dt max. and the calculated Vmax (dp/dt max = the speed of change in the intraventricular pressure in the left ventricle per time measured by the non invasive manometric technique).
- The end diastolic volume of the left ventricle is mostly raised. At the beginning, the end diastolic volume even when the compliance is increased, might be still normal. It rises later on as a result of the continuous worsening of the ventricular compliance.

In the course of few days the area of infarction becomes hard as a result of the deposition of fibrous tissue in this region of the heart. And the resulting reduction of compliance will eventually lead to the disappearance of the infarct dependent dyskinesis. This will eventually cause an improvement of the ventricular function. In the next there will be an establishment of a slow change in the ventricular geometry (remodelation) with the enlargement of the ventricular volume. This change, as well as the raise of the diastolic pressure in the ventricle will result in a raise of the myocardial oxygen requirement.

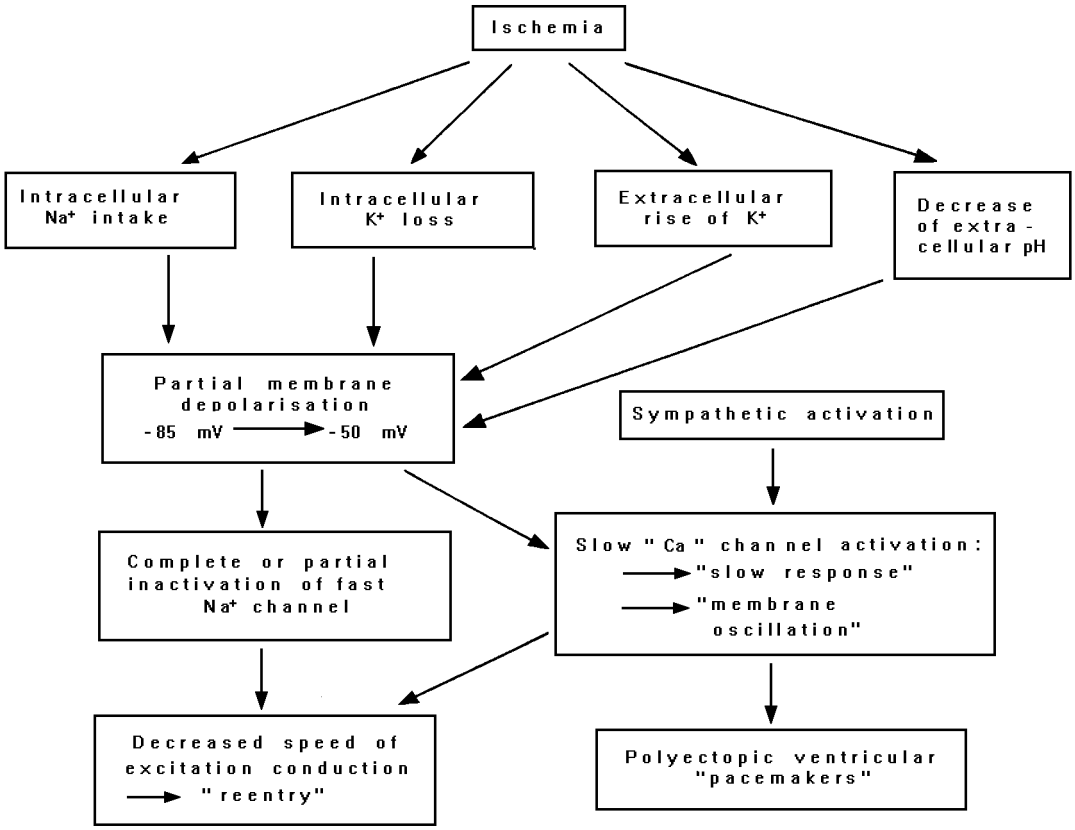

Figure 3.22: Pathogenesis of ischemic arrhythmias

From this point we would like to remind the student of the **electrocardiographical classification of the infarction**, that is referred to in the chapter of the electrical function of the heart. In cases of acute myocardial infarction a useful classification was made depending on what is known as the Q wave. We classify the infarction into Q infarction type (where we see a pathological Q wave on the electrocardiogram) and the other type is the non Q infarction (where the Q wave does not develop). The term Q infarction replaced the old term (transmural infarction). The morphological studies couldn't prove the specificity of the Q wave in that sense that it is the marker of the infarction which affects all the layers of the myocardial wall. The term non Q infarction replaced the old term (the subendocardial infarction). In the clinical practice we noticed that the number of patients with the non Q infarction is increasing. This might be due to the improvement of the diagnostic methods, as well as the new therapeutical procedures (calcium antagonists, nitrates, beta blockers), that limit the progression of necrosis. These patients appear electrocardiographically as if they have undergone a partial perfusion. They have smaller infarcts and a lower early mortality than the patients with the Q infarction. Yet these patients have a higher risk of developing an early infarction with its possible complication. Myocardial infarction might very rarely affect the atria or the right ventricle (this might occur in cases of their hypertrophy

which is the result of another primary disease).

Pathophysiological aspects in the therapy of acute myocardial infarction

1. From the awareness of the pathogenesis of the acute myocardial infarction we conclude, that an important therapeutic step lies in the reperfusion of the coronary field by the help of thrombolysis (via a chemical way, e.g. streptokinase as an infusion or a mechanical way e.g. PTCA = percutaneous transluminal coronary angioplasty).
2. Application of betablockers (intravenously or orally) is very useful mainly because they lead to a decrement in the oxygen requirement by the myocardium.
3. The use of an antiaggregatory substances (salicylic acid alone or in combination with dipyridamol) as a prevention of reocclusion of the coronary artery.

In the region of a palliative therapy the greatest attention is given to:

1. The reconstruction of the diseased coronary arteries (meanwhile the main problem is to overcome the restenotization of the artery in the region of the attempt, for example through the use of cellular proliferation inhibitors).
2. Changing the myocardial tolerance to the ischemia. Only recently it was found that, the myocardial tolerance to ischemia can be changed not depending on the perfusion at rest that is obtained by the collateral arteries. This tolerance could be trained by short occlusions of the coronary circulation (for 5-15 min.). It actually delays the occurrence of necrosis yet it does not prevent it. It was found that by this way it is possible to raise the gene expression for a whole series of proteins HSP 70, that have a protective function during many insults (such as heat, radiation). A high tolerance for ischemia is possible to imagine by the help of substances that are activated by the ischemia that would completely exclude the contractile apparatus of the myocardium during the earliest signs of ischemia (e.g. when pH drops). The spared oxygen will be then disposed for keeping the integrity of the myocardium.
3. Attempts made in the region of infarction healing. The modern moleculo-biological methods in animal experiments proved by the use of a cardio-specific genes to stimulate the cardiomyocytes to devide. It is hence possible to hope for the regeneration of the vascular system of the myocardium.
4. The hit in protecting the myocardium is what is known by preconditioning. In life the prevention must be sleep and glycosides, that can keep a high ATP level in the myocardium.

3.24 Pathophysiology of the brain circulation

Vascular supply of the brain

Brain is supplied by blood through 4 large vessels – 2 carotids and 2 vertebral arteries. The left carotid artery (a. carotis communis sinistra) is branching right out of the aortic arch, the right (a. carotis communis dextra) is branching from the brachiocephalic trunk. The carotid sinus lies at the level of C_3–C_4 where the common carotid artery branches into the internal and external carotid arteries. This sinus has special receptors for pressure changes (baroreceptors) and the afferent impulses travel through the glossopharyngeal nerve into the vasoregulatory centers. A. carotis interna enters the intracerebral cavity at the base of the skull through the carotid canal, then forms the S shape and passes through the sinus cavernosus. A. opthalmica which is the first branch of the internal carotid artery anastomosis with the a. carotid externa. Another branch of the internal carotid artery is a. communicans posterior. The internal carotid artery ends as a bifurcation into anterior and median cerebral arteries.

85 % of the blood supply of the brain is passing through the carotids and the rest through the **2 vertebral arteries**. The vertebral arteries in their extravertebral course (after branching from a. subclavia) are in close relation to the neck vertebrae.