This book is intended for experts, scientists and researchers who are just starting out in these areas of medicine. These are interdisciplinary and transdisciplinary areas from cardiology, orthopedics, oncology and some other medical fields. In this book, scientists have presented contemporary topics in the field of cardiology and cardiovascular diseases, the biggest public health problem of the modern world from which a large number of people die and fall ill. The presentation of sports cardiology is also very important, as well as the dangers to which recreational and professional athletes are exposed in order to achieve the best possible results. The chapters on breast cancer and the modern treatment of prostate hyperplasia are an outstanding presentation of some of the ailments of everyday life with modern treatment. And very interesting and valuable chapters on pneumothorax, unfortunately in today's everyday life with a completely new complication and COVID-19 infection, how to optimally treat osteoarthritis that significantly impairs the quality of life and something simple, yet so important question in pregnancy how to optimally compensate for iron deficiency.

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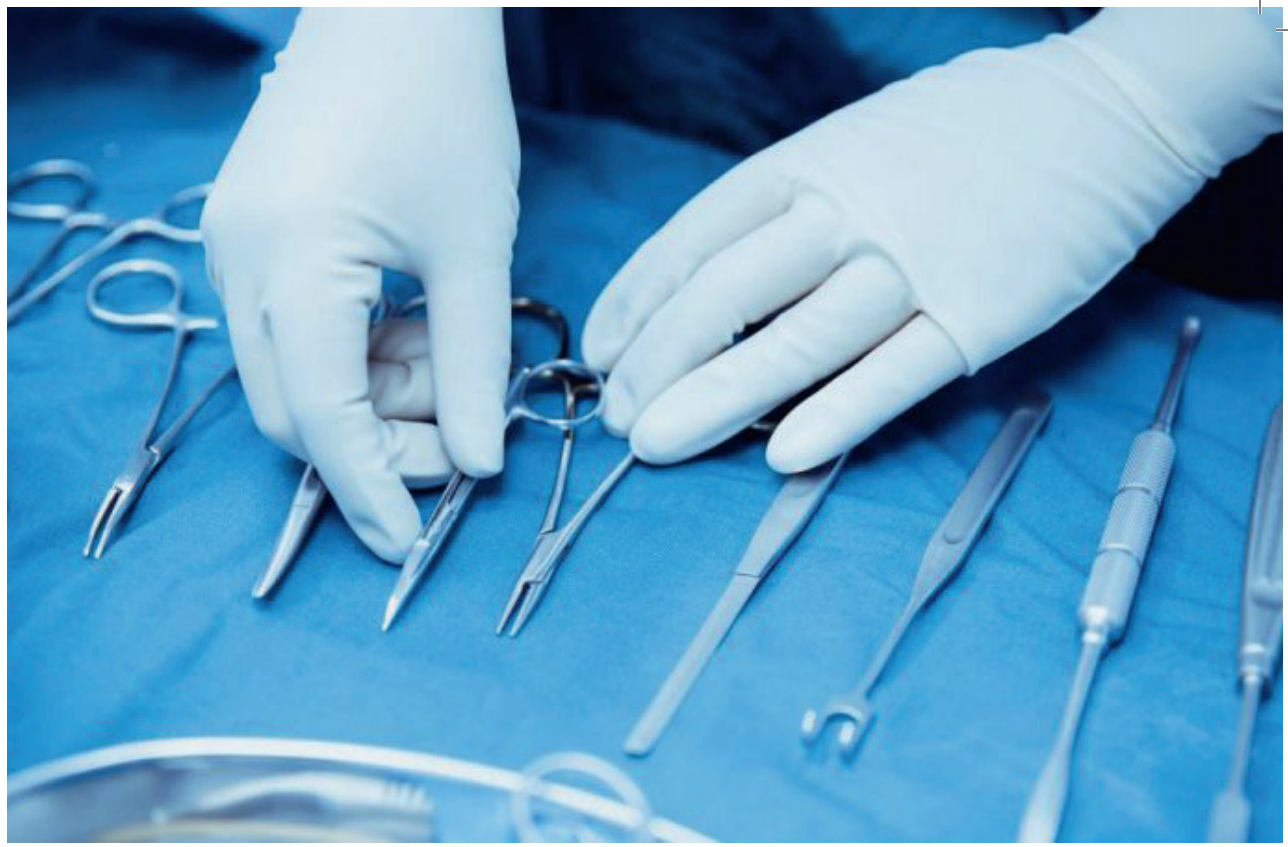

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DIAGNOSIS AND TREATMENT

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Asst. Prof. Antonija KRSTAČIĆ, MD.

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PREFACE

The new edition of scientific medical research in surgery and other areas of biomedicine represents another publishing endeavor. This book is intended for experts, scientists and researchers who are just starting out in these areas of medicine. These are interdisciplinary and transdisciplinary areas from cardiology, orthopedics, oncology and some other medical fields. In this book, scientists have presented contemporary topics in the field of cardiology and cardiovascular diseases, the biggest public health problem of the modern world from which a large number of people die and fall ill. The presentation of sports cardiology is also very important, as well as the dangers to which recreational and professional athletes are exposed in order to achieve the best possible results. The chapters on breast cancer and the modern treatment of prostate hyperplasia are an outstanding presentation of some of the ailments of everyday life with modern treatment. And very interesting and valuable chapters on pneumothorax, unfortunately in today's everyday life with a completely new complication and COVID-19 infection, how to optimally treat osteoarthritis that significantly impairs the quality of life and something simple, yet so important question in pregnancy how to optimally compensate for iron deficiency. We hope, that many medics will find useful and interesting content for their education and new research. The book has been reviewed and we want it to be as successful as the previous one.

Asst. Prof. Antonija Krstacic, MD.
Editor

Contents

CHAPTER I

INVESTIGATION OF THE EFFECT OF CARDIOVASCULAR DISEASE RISK FACTORS ON NERVE CONDUCTION VELOCITIES.

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Neuropathy is general term which refers to nerve damage due to various conditions. Peripheral neuropathy is a common condition in which nerves of peripheral nervous system are affected. Patients usually complain of tingling, numbness, burning, pain, particularly in the hands and feet. Symptoms usually depend on type of the nerve involved (sensory, motor, and autonomic). Prevalence of peripheral neuropathy has been reported as 2.4% in general population (1). Its prevalence raises to 8% in diabetic patients (2, 3). Despite thorough diagnostic evaluation, the cause of neuropathy cannot be found in about 10-18% of cases (4, 5).

Most common causes of neuropathy are diabetes mellitus, trauma, infections, alcohol and toxins. Oxidative stress, vascular abnormalities and microangiopathy have been accused in etiology of diabetic neuropathy (6, 7). Hyperglycemia, age, smoking, hypertriglyceridemia and alcohol consumption are major independent risk factors for neuropathy in diabetic patients (8). It has been shown that irrespective of hypertension diagnosis, diabetic neuropathy is associated with elevated systolic blood pressure (9). Further, this association persists even if disease duration is relatively short (10). In a many clinical situations, there is an association between neuropathy and ischemia or hypoxia. Incidence of neuropathy is higher in patients with chronic obstructive pulmonary disease and peripheral arterial disease (11, 12). Thus, atherosclerotic risk factors may play role in pathogenesis of neuropathy.

The aim of the present study was to evaluate effect of atherosclerotic risk factors on nerve functions.

1. Material and Methods:

A total of 354 patient files were screened Between June – September 2020 and 74 subjects were enrolled in the study. Subjects with ischemic heart disease, congestive heart failure, hypo-hyperthyroidism, renal and/or hepatic disease, diabetes mellitus, B12 deficiency, paraneoplastic neuropathy were excluded from the study. Ethical committee approval was obtained from local ethics committee.

Demographic characteristics and biochemical values were recorded from patient's files. All biochemical analyses were done after a 12-hour fast. Blood samples were drawn from antecubital vein with the patient in an upright position.

Median and ulnar nerves were stimulated at the wrist and their sensory responses were recorded 13 and 11 cm from the stimulation point, respectively. Sural nerve (SN) was stimulated at a distance 14 cm from lateral malleolus and its sensory response was recorded from behind the lateral malleolus. Electrical stimulation of superficial peroneal nerve (PN) was performed 14 cm proximal to recording electrode; which was located on the dorsal aspect of the foot. In sensory nerve conduction study, distal latency, amplitude of sensory nerve action potential and conduction velocity was evaluated.

For the median motor nerve conduction study, recording electrode was placed on the muscle belly of abductor pollicis brevis, median nerve (MN) was stimulated at antecubital fossa 7 cm proximal to electrode and compound muscle action potentials (CMAP) were elicited. Motor nerve stimulation of the ulnar nerve (UN) was done at 7 cm proximal to the active recording electrode, above and below elbow. CMAP amplitudes from abductor digiti minimi were taken for analysis. Tibial nerve (TN) was stimulated behind medial malleolus 9 cm proximal to active electrode and in the popliteal fossa. CMAP amplitudes were recorded from abductor hallucis muscle. Deep peroneal nerve (PN) was stimulated at (1) the ankle, 9 cm proximal to the recording electrode, (2) the fibular head and (3) the popliteal fossa. CMAP amplitudes were recorded from extensor digitorum brevis muscle.

2. Statistical Methods

Scale parameters were described by means and standard deviations, nominal parameters were described with frequency analysis. Spearman's rho correlation analysis was used for correlations. SPSS 17.0 for windows was used for analysis at 95% confidence interval.

3. Results

74.0% of patients were female and 26.0% were male. Mean age of the subjects was 60.16±10.04. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 139.49±27.21 and 82.30±13.88 mmHg, respectively. 9.6% of subjects were smokers, and 4.8% were using alcohol. Clinical and demographic parameters of the subjects are shown in Table 1.

Sensory latency of median nerve (MN) was positively correlated with age, smoking, SBP and DBP, LDL-C, glucose levels ($p<0.05$). Glucose was the most affecting parameter. Sensory velocity of MN was negatively correlated with age, smoking, SBP, DBP, and LDL-C level ($p<0.05$).Sensory latency of ulnar nerve (UN) was positively correlated with glucose level. Sensory velocity of UN was negatively correlated with age. Sensory amplitude of sural nerve (SN) was negatively correlated with SBP and LDL-C level. The most affecting parameter was SBP. Sensory latency of peroneal nerve (PN) was positively associated with age, LDL-C, glucose levels. Glucose level was the most affecting parameter. Peroneal amplitude was negatively correlated with age and SBP ($p<0.05$). The most affecting factor was SBP. Peroneal velocity was negatively correlated with age and glucose level. Effect of glucose level on peroneal velocity was higher. Spearman's rho correlation analysis results for sensory parameters are given in Table 2.

Motor latency of MN was positively correlated with SBP, BMI and glucose level. SBP was the most affecting parameter. Motor latency of UN was positively correlated with age, SBP, DBP, LDL-C, AKS levels and BMI. SBP was the most affecting parameter. Motor velocity of UN was negatively correlated with age, SBP, glucose level and BMI. Motor latency of SN was positively correlated with SBP, glucose level, and BMI. Glucose was the most effective parameter. Motor amplitude of SN was negatively correlated with age and SBP ($p<0.05$). SBP was the most affecting parameter. Motor latency of PN was positively correlated with SBP, LDL-C, triglyceride and glucose levels, glucose level being the most effective factor. Peroneal velocity was negatively correlated with age, systolic pressure, LDL and glucose levels. Spearman's rho correlation analysis results for motor parameters are given in Table 3.

4.Discussion

In this study we aimed to evaluate peripheral nerve functions by using electrophysiological measurements and found that cardiovascular risk factors, such as age, smoking, BMI, high blood pressure, high triglyceride, LDL-C and glucose levels were associated with impaired peripheral nerve function. Among these risk factors, SBP and glucose level seemed to have prominent role.

Electrophysiological studies play key role for quantifying peripheral nerve function. Improvements in nerve conduction study techniques and computer software programs have enabled us to obtain more detailed information about nerve physiology. Results of nerve conduction studies are objective, repeatable, sensitive, specific and correlated with clinical neuropathy (13)

A lot of research has implicated the cardiovascular risk factors as a potential cause of peripheral neuropathy. Diabetes, prediabetes and obesity have been shown as the main metabolic components associated with peripheral neuropathy in a United States population (14). Although the pathophysiology of diabetic neuropathy is not well understood, impaired blood flow and oxygenation have been thought as important factors for it (15). Ischemia and hypoxia that occur due to diabetes related vascular and metabolic abnormalities may cause peripheral nerve damage and hence diabetic neuropathy (16). Several studies have shown that hypertension had a relationship with the occurrence of diabetic neuropathy (17-19). Forrest et al. found that the most important factor for the development of distal symmetrical diabetic neuropathy was hypertension (18). Another study reported that diabetic sensory peripheral neuropathy had an independent relationship with diabetes duration, weight, age, retinopathy, albuminuria, height, insulin use and hypertension duration (19). Diabetic neuropathy incidence has been linked to high triglyceride levels, BMI, smoking and hypertension (15). These studies showed that hypertension is a risk factor for diabetic neuropathy. Hypertension is associated with decreased pain perception and there are some evidence about the role of hypertension in pathogenesis of peripheral neuropathy (20-22). Hypertension may be an independent risk factor for chronic symmetrical neuropathy in older patients (21). Diabetic and non-diabetic hypertensives had higher sensory perception thresholds than controls (22). Edwards et al. found that untreated hypertensives had lower sensory action potential amplitudes despite normal peripheral nerve conduction velocities (23). Teunissen et al. investigated cardiovascular disease prevalence and risk factors in chronic idiopathic axonal neuropathy patients along with neuropathic findings in peripheral arterial disease patients. In their study, chronic idiopathic axonal neuropathy patients had more cardiovascular disease and risk factors, and peripheral arterial disease patients had more neuropathy events than control groups (24). Recently, studies performed on diabetic patients found that patients with hyperlipidemia have significantly higher incidence of peripheral neuropathy (25).

In our study cardiovascular risk factors, namely age, obesity, smoking, LDL-C, glucose and triglyceride levels, influenced the motor and sensory nerve function. We think that this relationship is related to atherosclerosis. Atherosclerosis is a systemic disease which can affect any part of the

vascular bed. Oxidative stress, inflammation, endothelial dysfunction, vascular lumen stenosis and microcirculatory disturbances result in possible ischemia in peripheral nerves.

Peripheral neuropathy is highly prevalent condition, especially in older subjects. Although it is not fatal, severe symptoms may lead to decreased quality of life for some patients. Therefore better understanding of underlying mechanisms and risk factors could be an important step for its prevention and the development of new treatment modalities.

Conflict of interest: None

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Table 1: Clinical and biochemical variables of the subjects.

Parameter	Value
Gender, n (%)	
Female	54 (74.0)
Male	19 (26.0)
Age, mean ± SD	60.16±10.04
Smoking, n (%)	7 (9.6)
Alcohol, n (%)	4 (6.8)
SBP	139.49±27.21
DBP	82.30±13.88
TC	200.58±33.63
LDL	131.88±29.62
HDL	47.66±9.71
VLDL	25.19±11.52
TG	109.41±51.04
Glucose	94.16±16.42
BMI	26.36±4.01

BMI: Body mass index, DBP: Diastolic blood pressure, HDL: High density level cholesterol, LDL: Low density level cholesterol, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride, VLDL: Very low density level cholesterol.

Table 2: Correlation analysis results of sensory parameters.

Sensory Parameters	Median			Ulnar			Sura			Per		
	LT	AMP	VEL	LT	AMP	VEL	LT	AMP	VEL	LT	AMP	VEL
Age	**,355****	-,027	**-,282***	,228	,014	**-,251***	,098	-,222	,013	**,371****	**-,233***	**-,252**
Smoking	**,256***	,096	**-,251***	,067	,135	-,138	-,041	-,137	-,106	,143	-,142	-,141
Alcohol	,188	-,046	-,095	,138	-,008	-,018	,068	,054	-,054	-,125	-,097	-,004
SBP	**,362****	-,130	**-,446****	,179	-,134	-,218	,132	**-,354****	-,127	,206	**-,251***	-,047
DBP	**,315****	-,051	**-,344****	,192	-,007	-,194	,028	-,193	-,056	,147	-,191	-,046
LDL	**,358****	-,128	**-,261***	,088	-,049	-,159	,171	**-,314****	-,186	**,295***	-,160	-,207
Glucose	**,517****	-,055	-,196	**,352****	-,044	-,211	,294*	-,075	-,080	**,383**	-,172	**-0,29**
BMI	,223	,073	-,042	,228	-,129	-,153	,243*	-,039	-,048	**,337***	-,097	-,107

*p<0.05, **p<0.01

BMI: Body mass index, DBP: Diastolic blood pressure, LDL: Low density level cholesterol, SBP: Systolic blood pressure.

Table 2: Correlation analysis results of motor parameters.

Motor parmeter	Median			Ulnar			Sura			Per		
	LT	**AMP**	**VEL**	**LT**	**AMP**	**VEL**	**LT**	**AMP**	**VEL**	**LT**	**AMP**	**VEL**
Age	,190	-,125	-,148	**,265***	-,125	**-,276***	,219	**-,298****	-,147	,188	,009	**-,319****
SBP	**,374****	,035	-,210	**,486****	,014	**-,306****	**,314****	**-,347***	-,150	**,240***	-,067	**-,286***
DBP	,205	,117	-,073	**,362****	,038	-,072	,157	-,210	-,095	,115	-,067	-,182
LDL	,226	-,013	-,160	**,283***	-,009	-,087	,208	-,126	-,115	**,234***	,160	**-,410****
TG	0,23	-,138	-,162	,225	,003	-,110	0,2	-,071	-,072	**,239***	-,088	-0,16
Glucose	**,336****	-,075	-,188	**,318****	-,198	**-,241***	**,372****	-,059	-,167	**,389****	-,042	**-,238***
BMI	**,253***	,103	,074	**,307****	-,109	**-,269***	**,275***	-,216	-,023	,128	,114	-,170

*p<0.05, **p<0.01

BMI: Body mass index, DBP: Diastolic blood pressure, LDL: Low density level cholesterol, SBP: Systolic blood pressure, TG: Triglyceride.

CHAPTER II

SPORTS CARDIOLOGY

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1.Introduction

Today's sport expects top results from athletes, and in order to achieve great sporting success, athletes must train with extremely high intensity. The loads placed on the athlete require the adaptation of the organism to the efforts, and it includes the adaptation of the cardiovascular, respiratory and primarily the musculoskeletal system. In order to ensure the athlete's health, it is essential that each athlete undergo a detailed health examination that must be holistic and not focused on just one part. A medical examination should determine the athlete's general health and diagnose and examine any pathology if the examination reveals. Since sport does not only bring with it sports injuries in the form of musculoskeletal injuries, which is of course the most common, there can also be a problem with the cardiovascular system either due to heavy loads or if the athlete has a congenital heart defect that has not been previously diagnosed. Therefore, detailed cardiac treatment is very important for athletes in order to preserve the health of athletes and prevent sudden cardiac death, as the worst consequence.

2.Anatomy And Physiology of Heart Work

The structure of the heart

The heart is an organ located in the mediastinum and along with the brain is the most important organ in the human body. It consists of four chambers that perform the function of pumping blood into other organs

and tissues. The heart can be divided into a left heart and a right heart consisting of atrias and ventricles. Between the atria and the ventricles are atrial-ventricular valves that prevent blood from returning from the ventricles to the atria. On the left side of the heart is the bicuspid or mitral valve, named after the bishop's drop "mitral", while on the right side of the heart is the tricuspid valve. The function of the left side of the heart is to collect oxygenated blood that comes from the lungs through the pulmonary vein and flows into the left atrium, then passing through the mitral valve it flows into the left ventricle at the end of which is a large aortic blood vessel. By expelling blood through the aorta, the blood reaches other organs and tissues, which is why the left-sided circulation is called the systemic or large bloodstream. The function of the right side of the heart is to receive deoxygenated blood that enters the right atrium through the superior and inferior vena cava and then passes through the tricuspid valve into the right ventricle, which sends deoxygenated blood to the lungs for re-oxygenation by expelling it through the pulmonary artery. Therefore, the circulation of the right heart is called the pulmonary or small bloodstream.

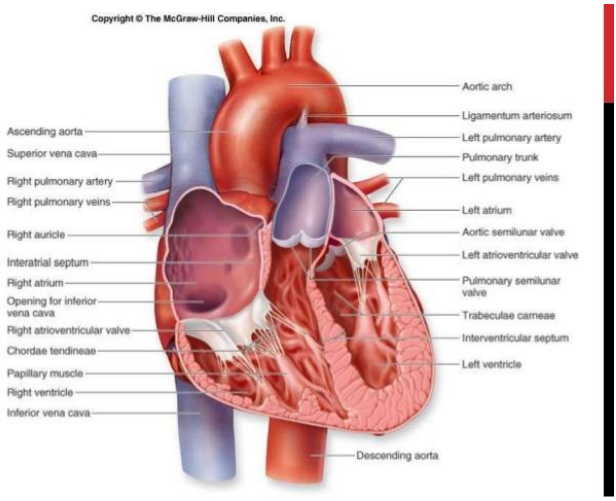

Figure1. Structure of the heart

The heart is made up of three walls, namely: the pericardium (outer layer), the myocardium (middle-muscular layer) and the endocardium (inner layer). The pericardium is a connective sheath that envelops the heart and consists of two leaves. The outer leaf consists of dense connective tissue and is attached to the tendon center of the shield and partly to the spine and large blood vessels coming out of the heart, while the inner leaf of the pericardium consists of a serous part and is attached to the heart surface. Between the inner and outer leaves of the pericardium is

a pericardial cavity containing a small amount of fluid that reduces friction between the leaves. The endocardium, like the pericardium, forms connective tissue, but unlike the pericardium, the endocardium is also covered with epithelial cells. The endocardium coats the entire interior of the heart as well as the heart valves, and continues into the endothelium of the large blood vessels. The myocardium is the middle layer of the heart wall, and at the same time a muscle without which the heart could not perform its basic function. It consists of three types of heart muscle: the atrial muscle, the ventricular muscle, and specialized excitable and conductive muscle fibers. Because their arrangement of actin and myosin fibers is very similar to that in skeletal muscle, the atrial and ventricular muscles contract in the same way as skeletal muscle, but with a much longer phase of contraction. The function of specialized excitable and conductive muscle fibers is the eruption of automatic electrical impulses and the conduction of action potentials through the heart, but their contraction is weak because they contain very few contractile myofibrils.

Electrophysiology of cardiac work

The work of the heart is manifested through the work of the heart muscle which "pumps" blood into various organs and tissues, in order to stimulate the myocardium to work at all, it needs an electrical impulse. This electrical impulse is created in the sinuatrial node or the so-called. SA-node, located in the posterior wall of the right atrium. The cells of the sinus node have the ability to generate electrical impulses, so they generate them rhythmically 60-80 times a minute in healthy people. Because the sinuatrial node is located in the right atrium, its cells are directly connected to the muscle fibers of the left and right atria and thus cause their contraction. An electrical impulse produced by the sinuatrial node by thin fibers reaches the interventricular septum near the right atrium where the atrioventricular node or AV node is located. The thin fibers between these two nodes conduct the impulse very slowly, so the impulses are retained and come to the ventricles only after the systole of both atria. This impulse retention allows the atria to empty normally and the ventricles to fill. The impulse after the atrioventricular node travels through the atrioventricular bundle, clinically called the His bundle to the upper part of the interventricular septum where it divides into left and right branches which then goes to the ventricles and ends up as Purkyni threads causing contraction of both ventricles.

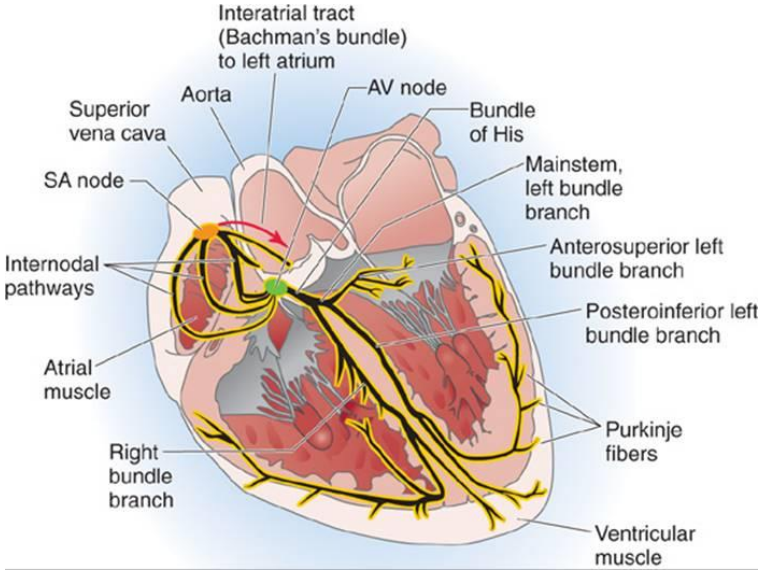

Figure 2. Representation of the electrophysiological system of the heart

The action potential of the heart muscle can be divided into four phases:

0. Depolarization phase - stimulation of the heart cell leads to the opening of voltage sodium channels that allow sodium to enter the cell and thus the depolarization of the cell itself

1. Initial repolarization phase - sodium voltage channels are closed, and potassium channels are opened through which potassium ions exit and thus initiate cell repolarization

2. The plateau-plateau phase of action potentials occurs after the initial repolarization as a result of the closure of potassium channels and the opening of calcium channels, ie reduced output of potassium ions, and increased entry of calcium ions

3. Rapid repolarization phase - includes closing of calcium channels and opening of slow potassium channels, thus ending the plateau phase and starting the phase of returning the membrane potential to the resting level

4. Phase membrane potential at rest - approximately -90mV

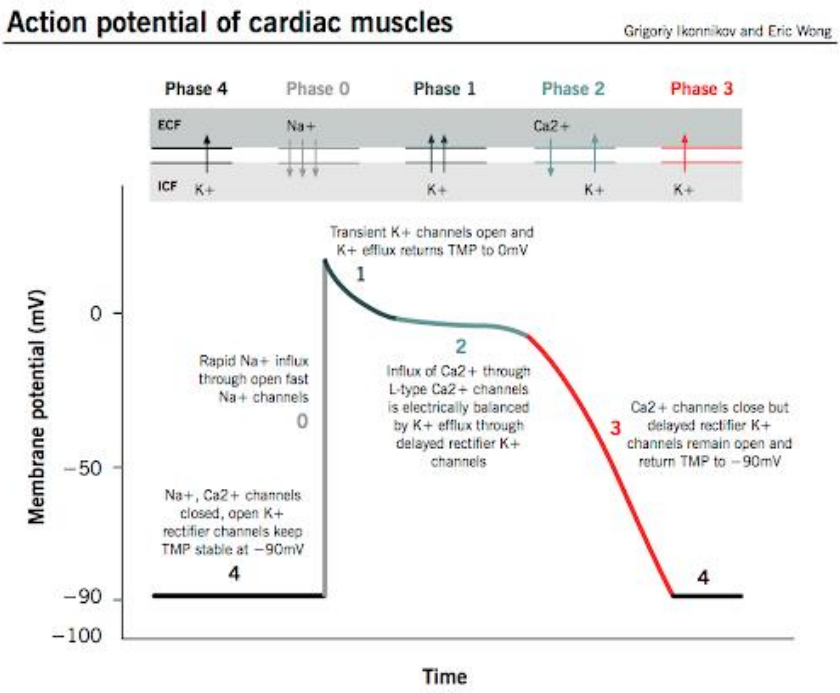

Figure 3. Phasis of action potential

3. The Role of The Cardiovascular System in Sports Activity

The role of the cardiovascular system in physical activity is based on the supply of nutrients and oxygen to the muscles. During sports activity, the diffusion capacity of the lungs is increased, which is manifested by greater blood flow through the lungs and thus allows faster gas exchange, which is important for biochemical aerobic processes to create ATP, which uses energy to gain muscle work. Thus, the cardiovascular system is the link between pulmonary ventilation and cellular oxygen consumption. A measure that demonstrates the ability to deliver oxygen during muscle work and cardiovascular endurance is oxygen consumption at maximum aerobic metabolism (VO2max).

Adaptation of the cardiovascular system is proportional to muscle requirements. Thus, the higher the intensity of training, the higher the hemodynamic parameters. During rest, 15-20% of the minute volume goes to the muscles, while during intense physical activity this percentage can reach up to 80-90%. With an increase in cardiac output, the heart rate and stroke volume increase, which affect changes in cardiac output. The stroke volume in athletes with high cardiorespiratory abilities is significantly higher at rest and during maximum load when the stroke volume can be up to 200 ml per beat. Of the structural adjustments, the most significant is

left ventricular hypertrophy, which is most exposed to stress and occurs in athletes who engage in sports that require endurance. During exercise, blood is redirected to the areas where it is most needed. In high-endurance training, the contracting muscles utilize 80% or more of the blood flow, while the flow in the liver and kidneys decreases. In contrast to exercise, during rest the muscles consume only 15-20% of the blood flow, while the liver and kidneys utilize half.

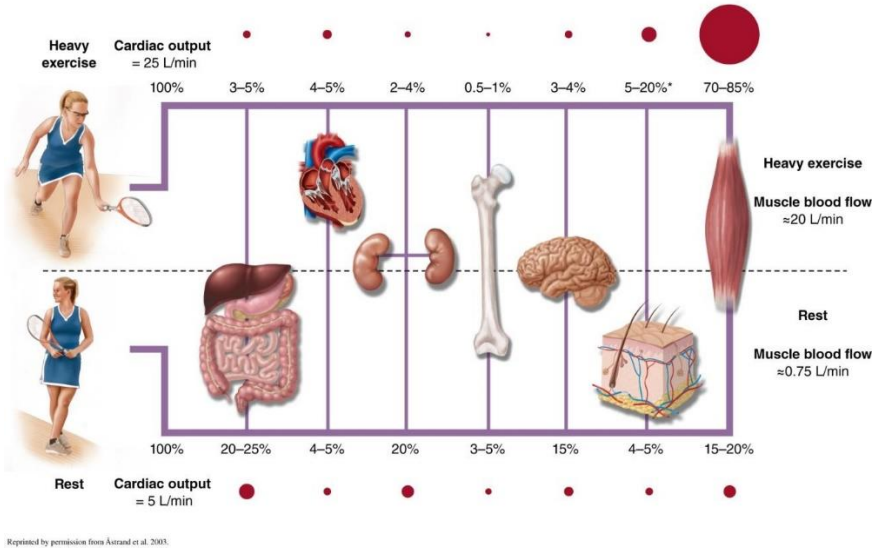

Figure 4. Distribution of blood flow during sports activity

Some studies have shown that hemodynamic parameters, structural, and functional adjustment of the heart can vary depending on the type of sport, which may be dynamic or static. Nowadays, it is difficult to say for a sport that it is predominantly static or dynamic, because athletes use different training approaches to improve their physical fitness. Close to an ideal example for a dynamic sport is long-distance running, while for a static sport an example is bodybuilding and weightlifting.

In athletes who predominantly engage in dynamic sports, an increase in the inner diameter of the left ventricle was observed by about 10%, while in athletes engaged in static sports or strength exercises, an increase of 2.5% was observed. In sports that required dynamic and static exercises and long-term training such as cycling, the wall thickness of the left ventricle was significantly more pronounced than in runners. The probable interpretation of these results is that the development of so-called eccentric or concentric left ventricular hypertrophy according to the type of sport cannot be considered an absolute or dichotomous concept, because training regimes and sports activities are not exclusively dynamic or static.

4. Cardiological Examination and Diagnosis in Athletes

History and examination

Cardiac examination of athletes places emphasis on the prevention of sudden cardiac death which is the leading cause of death in younger people (<35) during physical exertion. Therefore, cardiac treatment is important to identify undiagnosed conditions and adequately care for conditions that are already known. Guidelines for the cardiac examination of athletes were issued by the American Heart Association and European Society of Cardiology. After anamnesis and physical examination we usually perform ECG and echocardiography.

Electrocardiogram (ECG)

An electrocardiogram is a non-invasive cardiac diagnostic test that records the electrical activity of the heart. Athletes often experience changes in the ECG due to repeated exertion that causes electrical and structural adjustments that may overlap or suggest cardiovascular disease. Therefore, it is important to properly record and interpret the ECG findings to see if it is a pathological or normal physiological process. If the ECG finding is misinterpreted the athlete may be disqualified and may be referred to expensive diagnostic procedures that are unnecessary. Contrary to this situation, a misinterpretation of the ECG can replace the pathological process with a physiological one and put the athlete at great risk of a heart attack. Physiological adjustments of the autonomic nervous system of the heart, most commonly caused by increased vagal tone, cause changes in the athlete's electrocardiogram. Approximately 80% of athletes experience changes such as early repolarization, sinus bradycardia, or first-degree atrioventricular block. For example, athletes in endurance sports such as cycling and rowing have been shown to develop significantly greater changes on the electrocardiogram in the form of higher QRS voltage or sinus bradycardia compared to sports that do not require endurance but require strength and speed. Such changes on the electrocardiogram are due to higher heart capacity and left ventricular thickness. Most cardiac conditions that can lead to sudden cardiac death in young athletes are often asymptomatic and therefore not detected in time. The Italian screening experience, which lasted 25 years, concluded that in addition to physical examination of athletes, electrocardiogram recording should be included because it has significant value in detecting cardiac conditions and diseases that can lead to sudden cardiac death in asymptomatic athletes.

Echocardiography

Echocardiography or ultrasound of the heart is a non-invasive diagnostic imaging method used to detect morphological changes in the

heart. In sports cardiology, echocardiography can complement cardiac examination in two areas: screening before participating in sports and analysis of cardiac adjustments induced by training. The usefulness of echocardiography has been demonstrated in the differential diagnosis of various diseases that can cause sudden cardiac death, with special emphasis placed on left and right ventricular analysis. After all, some changes in the heart can be missed by physical examination and electrocardiogram, and can be easily diagnosed by echocardiography. The most common changes diagnosed by echocardiographic findings are divided into two groups, namely: physiological structural and functionally adaptive cardiac changes. Therefore, echocardiography can distinguish between physiological changes caused by training and pathological changes such as hypertrophic cardiomyopathy that can be the cause of sudden cardiac death. One 2013 study compared Doppler echocardiographic findings in soccer players, long-distance runners, and cyclists with the findings of the non-sports population, and the purpose of the study was to assess cardiac structure and function. The findings showed that athletes from these sports had a larger left atrial volume, left ventricular thickness, and diastolic diameter of the right and left ventricles as opposed to non-athletes. Among athletes, cyclists have been shown to have greater structural changes than footballers and runners. The systolic function of the left atrium recorded by Doppler technique did not show significant differences in athletes, while the systolic function of the right ventricle was higher in cyclists and football players compared to runners.

5. Cardiological Conditions and Diseases in Athletes

Sports heart

Sports heart is one of the scientific issues that sparked discussion among scientists for the reason that one part of them believed that sports heart is healthy heart, ie the heart adapted to constant intense loads, while the other part considered it to be cardiac pathology. But in 1889, the Swedish physician S. Henschen described hypertrophic changes in the heart in Nordic skiers caused by high load. Athletic heart is a physiological condition found in athletes who train at high intensity for more than five days a week for a minimum of one hour. Sports heart involves hypertrophy of the heart itself, as well as enlargement of the heart cavities and thickening of the myocardial wall leading to an increase in cardiac output which consequently results in a decrease in resting heart rate. Such adaptation of the heart to exertion allows for a greater minute volume which is very important for the supply of skeletal muscle with nutrients and oxygen, i.e. the more minute volume the larger skeletal muscle will receive more nutrients and oxygen. The sports heart can easily be confused with a pathological process and it is therefore important to recognize

whether it is physiological hypertrophy or pathological. If the sports heart is replaced with pathological hypertrophy, it can cause severe consequences in athletes who continue with high-intensity training. Therefore, detailed cardiac treatment of athletes is important to prevent side effects.

The diagnosis of sports heart is made on the basis of anamnestic data, clinical examination, electrocardiography (ECG) and other specific diagnostic tests if necessary in order to complete the clinical examination and remove the suspicion of a pathological condition. The sports heart is often asymptomatic, and is therefore only detected during routine examinations of athletes. Some athletes, however, develop some symptoms that are associated with adaptive changes in the heart, and may even suggest some heart disorder.

Cardiomyopathies

Cardiomyopathies are diseases of the heart muscle that can be inherited or acquired. According to the classification of the European Society of Cardiology, cardiomyopathies are classified into several groups:

1. Hypertrophic cardiomyopathy
2. Dilated cardiomyopathy
3. Arrhythmogenic dysplasia of the right ventricle
4. Restrictive cardiomyopathy
5. Unclassified cardiomyopathies

In sports cardiology, hypertrophic cardiomyopathy and arrhythmogenic dysplasia of the right ventricle are of the greatest importance, because they are the largest cause of death in young athletes.

Hypertrophic cardiomyopathy has been cited in numerous statistical analyzes as the leading cause of sudden cardiac death in athletes under 35 years of age. Left ventricular hypertrophic cardiomyopathy is the most common form of cardiomyopathy in athletes whose diagnosis is very challenging because it should be clearly distinguished whether it is a pathological hypertrophy or a physiological one caused by intense training. Because hypertrophic cardiomyopathy is the most common cause of death in athletes, the American Heart Association and the European Society of Cardiology have issued recommendations banning competitive sports with medium and high dynamic or static loads.

Dilated cardiomyopathy is characterized by dilatation and systolic dysfunction of the left ventricle, and its differential diagnosis can be difficult because a large proportion of athletes engaged in endurance sports show dilatation of the left ventricle. The diagnosis of dilated cardiomyopathy is made on the basis of these indicators: systolic function of the right ventricle with ejection fraction below 45%, right ventricular dysfunction, regional wall irregularities, positive family history, changes in the electrocardiogram in the form of wave inversion or some other

disturbances and tests such as magnetic resonance imaging and echocardiography are also very useful. Athletes who have dilated cardiomyopathy are considered to be at high risk for sudden cardiac death, and according to European and American cardiologist recommendations, such athletes should be excluded from competitive sports activities.

Arrhythmogenic dysplasia of the right ventricle is a disease characterized by the finding of fibrous and fatty tissue in the myocardium of the right ventricle, and can extend to the left ventricle and consequently can cause ventricular tachycardia and sudden cardiac death. It is diagnosed using non-invasive and invasive medical procedures that assess heart rhythm and structure. Treatment is based on the prevention of sudden cardiac death by the use of antiarrhythmic drugs, and in the more severe phase by the use of an implantable cardioverter defibrillator. Athletes with diagnosed arrhythmogenic dysplasia of the right ventricle are recommended to engage in sports of reduced intensity.

Athletes with any diagnosed cardiomyopathy should be excluded from high-intensity competitive sports, and exceptionally some athletes may engage in low-intensity sports such as golf or billiards. The ban on competition also applies to asymptomatic athletes who have been diagnosed with any form of cardiomyopathy, regardless of whether they use some form of treatment or not.

Myocarditis

Myocarditis means inflammation of the heart muscle, which can later lead to heart dysfunction and arrhythmias. The most common type of myocarditis in the world is viral myocarditis, while in young athletes the presence of toxins such as catecholamines and cocaine should be examined first during the examination. Although myocarditis is not very common unlike other heart diseases, it accounts for 5-22% of sudden cardiac deaths in younger athletes. It is believed that the onset of myocarditis first involves suppression of the athlete's body in response to intense physical exertion during training. Excessive inflammatory response of the body can lead to deterioration of the myocardium and skeletal muscles and catabolism due to lack of necessary energy.

The cause of myocarditis in athletes can be different depending on the type of sport in which the athlete is engaged. For example, contact sports such as boxing develop a higher risk of transmitting droplet infections, orienteering sports such as orienteering run have a higher risk of developing an infection such as ticks. According to the recommendations of the European Society for Preventive Cardiology (EAPC) and the American Heart Association (AHA), athletes with myocarditis should be excluded from competitive and amateur sports activities for six months. After six months, athletes with myocarditis should be evaluated before continuing with sports activities that must

initially be weaker. It is important for professional athletes to state the duration, intensity, frequency and mode of activity, as they have a different perception of lower physical activity as opposed to the rest of the population.

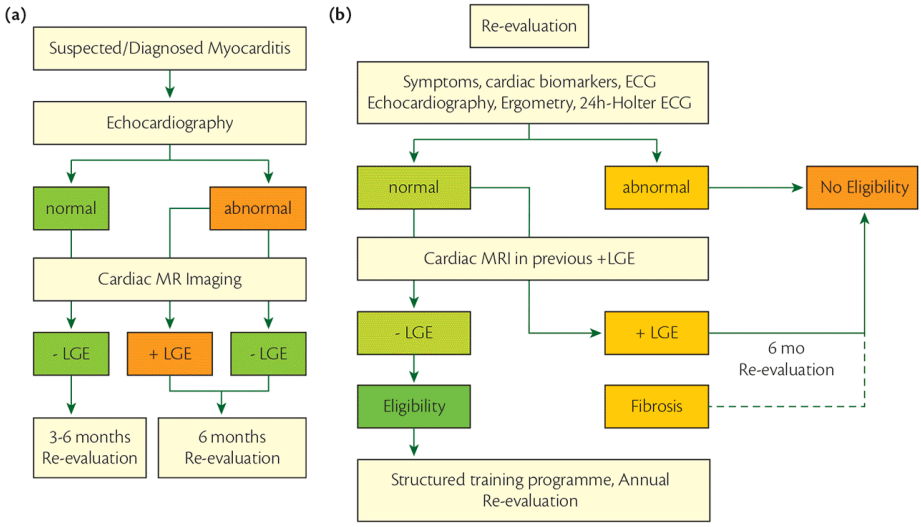

Figure 5. Assessment of myocarditis (a) and ability to play sports after 6 months (b)

Congenital heart defects

Congenital heart disease is a congenital defect, which can limit some athletes from playing sports. The most common congenital heart defects include ventricular septal defect, atrial septal defect, and open ductus arteriosus. Since there is no demonstrative evidence that these forms of heart defects cause sudden cardiac death, if children with these congenital heart defects do not have significant changes in hemodynamic parameters, they can continue to play sports. If congenital heart defect is accompanied by pulmonary hypertension that causes significant hemodynamic changes, acute symptoms may occur that reduce the ability to exercise, lead to chest pain, cause syncope or arrhythmias, and may result in sudden cardiac death. In untreated ventricular septal defect, it is recommended that athletes with a small ventricular septal defect with normal heart size and without pulmonary hypertension can participate in all sports, and in the case of a large defect, surgical intervention is required. After treatment for 3-6 months, asymptomatic athletes may engage in sport if pulmonary hypertension, atrial or ventricular tachyarrhythmia, or myocardial dysfunction are ruled out. For untreated atrial septal defect, it is recommended that in minor defects (<6 mm) with normal right heart volume and confirmed pulmonary hypertension, they should not

participate in competitive sports, while in major defects without pulmonary hypertension, sports are recommended. If the treatment is performed, athletes without pulmonary hypertension, arrhythmia or myocardial dysfunction can continue playing sports for 3-6 months after the intervention. Athletes with small untreated ductus arteriosus, normal left heart dimension and pulmonary artery pressure can play sports, and in moderate or large defects with persistent pulmonary hypertension and enlarged left ventricle, temporary exclusion from sports is recommended until the defect closes.

Valve diseases

Nowadays, the incidence of heart valve disease, the so-called valvular disease is on the rise in both the elderly and the younger. Changes that occur in the heart valve caused by a pathological process are stenosis of the natural flow of blood and a disorder in the one-way flow of blood through the heart valve.

The most common cause of mitral stenosis is rheumatic fever, which in turn causes fibrosis and calcification of the heart valves, and the tendon cords shorten and thicken. The hemodynamic consequences that occur due to mitral stenosis cause a decrease in blood flow and thus minute volume and an increase in left atrial pressure in diastole to increase minute volume. Due to the insufficiency of the mitral valve, the phenomenon of mitral regurgitation occurs, which means the return of blood from the ventricles to the atria.

Aortic stenosis can occur below, above or on the valve itself, so we distinguish between supvalvular, supravalvular and valvular aortic stenosis. The most common aortic stenosis is valvular, which can be the result of rheumatic fever, atherosclerotic changes and degenerative calcifying process, and the basic hemodynamic feature is the difference between the pressures of the left ventricle and the aorta. Aortic insufficiency is characterized by damage to the valves, so the valves leak blood back to the left ventricle. The most common causes of aortic insufficiency include infectious endocarditis and aortic prosthesis dysfunction, while less common causes may be arterial hypertension, trauma, or aortic dissection. Athletes suspected of having valvular disease should have an echocardiographic examination to see the function of the heart valves and the flow of blood through them. Those athletes who have mild to moderate mitral and aortic regurgitation without structural changes in the form of atrial or ventricular dilatation have no barriers to further exercise, while severe forms of regurgitation require exclusion from competitive sports and corrective surgical intervention.

Athletes with conduction disabilities

Sinus rhythm disorder in athletes includes asymptomatic bradycardia whose frequency is usually between 40-50 beats. Bradycardia

occurs in athletes due to neurovegetative changes caused by intense training, and especially in sports that require high aerobic capacity such as cycling and marathon. Severe bradycardia is rare, but can be found in older athletes over the age of 40 during the night. Bradycardia occurs physiologically in athletes in response to exertion, so it is considered a benign phenomenon if it is asymptomatic and if the heart rate increases normally during sports activity.

Early repolarization is considered by athletes to be a benign phenomenon caused by increased vagal tone as a result of intense training. Athletes who have asymptomatic early repolarization but an increased risk detected by a family history need to undergo additional cardiac treatment to rule out J wave syndrome. Since intense training leaves changes on the autonomic nervous system and thus on the primary ion channels, the fact cannot be ruled out that early repolarization can cause arrhythmias. Most athletes develop early repolarization with a growing ST segment, but the prevalence of malignant early repolarization has also increased including subtypes that may increase the risk of arrhythmias, such as inferior J waves and J waves that may be accompanied by a horizontal or descending ST segment. A study conducted for 90 days in rowers and football players showed that the prevalence of early repolarization increased in endurance sports, ie rowers, and remained the same in football players and strength sports.

In addition to sinus bradycardia and early repolarization, first-degree atrioventricular block is one of the most common changes in an athlete's electrocardiogram. First-degree atrioventricular block is often seen in athletes, and is marked by PQ prolongation at the electrocardiogram finding and leaves no specific consequences. If the PQ interval on the electrocardiogram is extended by more than 0.3 seconds and the QRS complex is altered, additional diagnostic processing such as ergometry, 24-hour holter electrocardiogram, and echocardiography should be performed to suspect possible structural heart disease. Asymptomatic athletes who do not experience a worsening of the PQ interval during exercise can engage in all sports, and if structural heart disease is detected during additional diagnostic processing then sports activity depends on the disease itself.

The second stage block, the so-called The Mobitz I type or Wechenbach block is often found in highly trained athletes due to increased vagal tone and does not carry significant consequences for the athlete. The diagnostics used to detect this condition are an electrocardiogram, a 24-hour holter electrocardiogram and ergometry, and some athletes also use a heart rate monitor during training. The electrocardiogram is characterized by a prolonged PR interval, a blocked P-wave, and a discharged QRS complex. If a branch block is diagnosed in the electrocardiogram finding, an electrophysiological examination should be performed to detect the level of conduction disturbance. Asymptomatic

athletes who have a structurally healthy heart or some of the structural defects of the heart, and with stagnant or improved atrioventricular conduction are allowed to engage in all types of sports. Whereas in asymptomatic athletes who develop a first-degree block during or after exercise, the intensity of training should be reduced, and such athletes should be additionally electrophysiologically examined.

A second-degree Mobitz II-type block is characterized by a conduction disturbance below the level of the atrioventricular node, usually at the level of the His bundle. It is recognized on the electrocardiogram by intermittent non-conducting P-waves. It occurs very rarely in athletes, but if an athlete has this conduction disorder, he needs the implantation of a permanent pacemaker before sports activities.

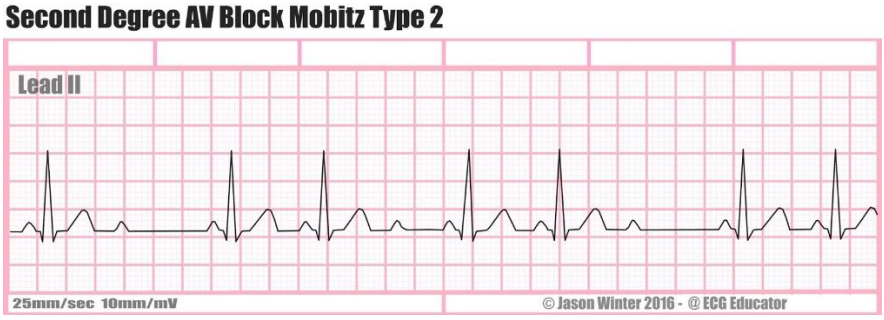

Figure 6. AV block second degree Mobitz type 2

Third-degree block or total atrioventricular block denotes an abnormal heart rhythm resulting from impaired conduction through the atrioventricular block. That is why the atria and ventricles knock separately, because the atria are led by the sinuatrial node, and the ventricles by one of the distal latent conductors, which later cause atrioventricular dissociation. Athletes who have a third-degree block should be excluded from competitive sports and need a pacemaker implant.

Arrhythmias

Most arrhythmias that occur in athletes occur due to undiagnosed cardiac structural changes and canalopathy. Signs of arrhythmia include morphological changes and changes in the electrocardiogram, and symptoms are often overlaid by morphological changes caused by training. The most significant arrhythmias are divided into supraventricular tachycardias and ventricular extrasystoles and ventricular tachycardias. One of the most common arrhythmias that occurs in athletes is atrial fibrillation, which belongs to the group of supraventricular tachycardias and is often associated with sports that require endurance.

The mechanism of atrial fibrillation is unclear, but it is assumed that there are three causes, namely a specific trigger that includes atrial ectopia,

sports supplements and illicit drug use, then a substrate caused by genetic predisposition, inflammation, fibrosis and heart remodeling and a modulator that includes autonomic activation, electrolyte disturbance, and gastroesophageal reflux. Treatment of atrial fibrillation initially requires a reduction in physical activity because temporary interruption can reduce or prevent recurrence of atrial fibrillation. Some athletes also need treatment with antiarrhythmics, but speed control agents, such as beta-blockers or calcium channel blockers, that may impair the athlete's performance should be avoided.

The second group of arrhythmias includes monomorphic or catecholaminergic polymorphic ventricular tachycardia and ventricular extrasystoles. Monomorphic ventricular tachycardia is a fairly common occurrence in athletes that most commonly occurs as benign as part of physiological changes occurring in the athlete's heart, however it can also occur as idiopathic and may not be associated with athlete status. Monomorphic ventricular tachycardia is often asymptomatic and is usually detected by electrocardiogram or cardiac treatment of symptoms, most often palpitations. Although monomorphic ventricular tachycardia is most often benign, it is important to identify all factors that may indicate structural heart disease and to reduce athletic activity to prevent sudden cardiac death.

Catecholamineric polymorphic ventricular tachycardia is rare and is often associated with hypertrophic cardiomyopathy and coronary anomalies and has been identified as a cause of sudden cardiac death. It most commonly occurs as syncope during emotional stress or intense physical activity in the presence of palpitations. All forms of ventricular tachycardia are treated with beta-blockers, and athletes are advised to discontinue competitive sports.

Ventricular extrasystoles are relatively common in athletes, and some studies have even shown that the incidence of ventricular extrasystoles is higher in highly trained athletes compared to the population engaged in recreational sports. Ventricular extrasystoles are not considered a risk for ventricular tachycardia or sudden cardiac death, and they occur in both structural heart disease and those who do not have structural heart disease. In a study by Biffi and colleagues who investigated the incidence of ventricular extrasystoles in athletes who had about 2,000 ventricular extrasystoles in 24 hours, it was shown that deconditioning athletes within 3 months can reduce the number of ventricular extrasystoles in 24 hours.

Heart comfort

Heart coma or heart agitation in athletes most commonly occurs in ball sports such as baseball, and can be caused by a blow to the ball or part of the body in the left chest area. When struck in the left side of the chest,

the myocardium deforms and thus causes ventricular fibrillation, which in turn causes sudden cardiac death despite the normal structure of the heart and thus represents an emergency. If the stroke occurs during ventricular repolarization, the change on the electrocardiogram occurs in the form of a high T-wave, and if the stroke occurs later it is likely to result in an elevation of the ST segment, transient tostal heart block, or left branch block. Heart convulsions, although very rare with cardiomyopathies, are the leading cause of death, especially in childhood athletes. Therefore, a register of heart commotion has been launched in the United States, with an average reported age of 15, and a very small number of athletes are over the age of 20, which may be the cause of thinner chest wall thickness in children compared to adults. Since cardiac compression is characterized by ventricular fibrillation, the first step in treatment should be directed towards early defibrillation and cardiac massage, and if resuscitation is continued, medications to increase coronary perfusion flow and ventilation accessories should be introduced. If dull cardiac trauma has occurred that has caused dysrhythmia, treatment is based on stabilizing the electrical activity of the heart. Survival rates after cardiac compression improved, thanks to timely and early outpatient resuscitation for both other cardiac arrest and cardiac compression.

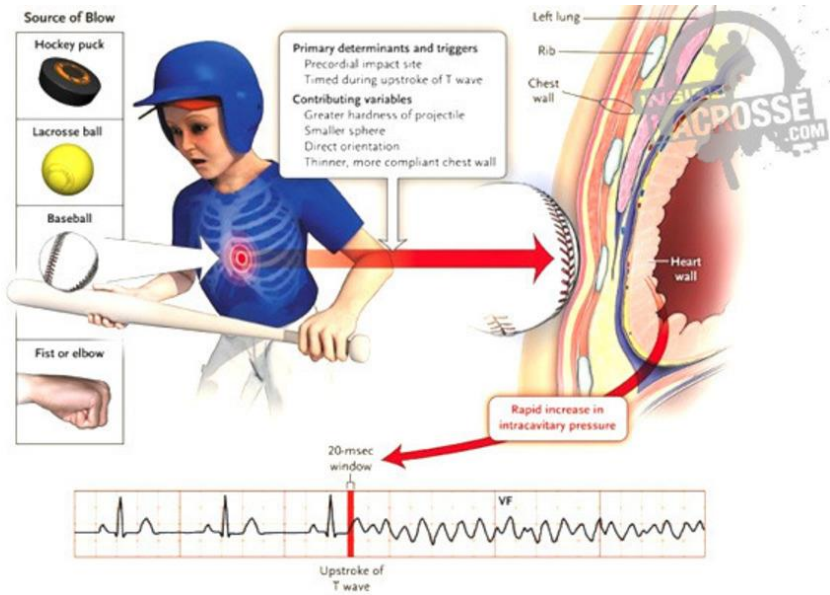

Figure 6: Heart confort and mechanism of injury

6.Sudden Heart Death in Athletes

Sudden cardiac death is the most common medical cause of athlete death, although its very rare occurrence in athletes leaves long-lasting emotional and social consequences on the athlete's environment.

Therefore, considerable efforts are being made to identify and understand as early as possible the causes that lead to sudden cardiac death. The definition of sudden cardiac death in athletes varies because some incidence estimates include only death during exertion or shortly after exertion, most often within one hour, while other estimates include death of athletes outside of exertion.

The most common causes of sudden cardiac death in athletes are due to:

Congenital diseases :
Structurally altered heart
Hypertrophic cardiomyopathy
Congenital long QT syndrome
Arrhythmogenic dysplasia of the right ventricle
Catecholaminergic polymorphic ventricular tachycardia
Dilated cardiomyopathy
Wolf-Parkinson-White syndrome
Brugada syndrome
Congenital anomalies of the coronary arteries
Ionic canalopathy
Aorthopathy
Valvular diseases

Acquired diseases
Coronary atherosclerotic disease
Heart convulsions
Kawasaki disease
Acquired prolonged QT wave
Myocarditis
Other environmental factors and substances

Since 1966, 1101 cases of sudden cardiac death have been reported in athletes under 35 years of age. The largest share is carried by cardiovascular diseases, of which 50% were caused by cardiomyopathies and congenital heart diseases, and 10% by atherosclerotic altered coronary vessels. In young athletes, the fact is that 90% of cases of sudden cardiac death occur in training or competitions that can be caused by physical exhaustion that can consequently cause pathological arrhythmias. The incidence of sudden cardiac death depends on the athlete's general health and the type of sport he is engaged in. In older athletes, the most common cause of sudden cardiac death is atherosclerotic altered coronary blood vessels, while in younger athletes, the most common cause is congenital heart defects. It is very difficult to detect a quality screening system that will be able to identify all the factors that can cause sudden cardiac death in athletes, so today there is increased access to automated external

defibrillators and increased education as well as the importance of community-based cardiopulmonary resuscitation. prevented sudden cardiac deaths on sports fields.

7.Conclusion

Nowadays, when medicine has advanced tremendously, it is possible to diagnose and treat almost all cardiovascular diseases. The vast majority of young athletes are asymptomatic, so a detailed personal and family history is very important, which is the first step towards the diagnosis of heart disease, then a physical examination and electrocardiogram, which are the basis of diagnosis, but if necessary, athletes can be sent for additional cardiac treatment. on the diagnosis and general condition of the athlete, a decision is made on whether the athlete can continue to play sports or not. It is far better to detect heart disease as soon as possible in order to start treatment on time, and thus reduce the possibility of sudden cardiac death. However, some heart diseases require athletes to stop playing sports, which can cause a negative emotional reaction in athletes, but the health of the athlete must come first. If an athlete is diagnosed with one of the inherited heart diseases, a life can potentially be saved for a close family member.

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CHAPTER III

CARDIOVASCULAR DISEASES AND PREVENTION

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1.Cardiovascular Diseases

Cardiovascular diseases (CVDs) that consist of stroke, heart attack and other numerous cardiac and vascular conditions are the leading global cause of premature mortality and an important factor, which decreases quality of life (GBD 2017, Kumar et al. 2009). CVDs are actually a collection of diseases affecting the heart, blood vessels of the heart and the brain. In 2017, 18.8 million people died from CVDs worldwide (GBD 2017). According to the data of the Turkish Statistical Institute (TSI), CVDs was the leading cause of deaths in Turkey in 2016, accounting for 39.8% of all deaths (TSI 2016). According to the data reported by the Turkish Study of the Incidence of Chronic Diseases and Risk Factors (TKrHRF), the incidence of CVDs was found as 3.8% in men and 2.3% in women, but this rate raised up to 19.6% in men and 10.8% in women aged over 75 years (Unal and Ergor 2013). It is estimated that by 2030 annual medical costs associated with CVDs will rise to 1,044 USD (Mozaffarian et al. 2016) The consequences of these diseases are even worse in the developing countries (WHO 2004). According to the World Health Organization (WHO), over three quarters of deaths from CVDs occurs in low- and middle income countries (WHO 2017). Many types of CVDs occur as a complication of atherosclerosis.

1.1.Atherosclerosis

Atherosclerosis is a multifactorial chronic and inflammatory disease characterized by arterial stenosis and occlusion as a result of the disruption of the flexibility of the arteries (Yusuf et al. 2004, Khera & Kathiresan, 2017). It is a disease of arterial vasculature characterized by an imbalance and abnormal accumulation of inflammatory cells, matrix deposits and lipids in the walls of the medium and large arteries (Mota et al. 2017). Atherosclerosis is especially prevalent in the developed countries, but its incidence is rapidly increasing also among the populations in the developing countries (Herrington et al. 2016). Atherosclerosis begins in

the early periods of life (most commonly the second decade), but does not manifest until thrombotic complications such as coronary syndromes and stroke (Charakida et al. 2006). It is a complex pathological process occurring in the walls of the vessels over years. In this complex process, deposits (plaques) in the medium and large arteries cause the inner surface of the vessels to become irregular and the lumen of vessels narrows. Eventually the deposit (plaque) can rupture, leading to formation of a blood clot. When this clot occurs in a coronary artery, it can cause a heart attack, and if it occurs in the blain, a stroke may occur. In a heart attack, blood supply is interrupted due to the diseases of the vessels supplying the heart, which in turn lacks oxygen and nutrients to fuel its muscular contractions and pumping function. In a stroke, the same type of condition occurs in the brain, and lack of oxygen disrupts its normal functioning. Heart attacks and strokes are acute life threatening events mainly caused by a blockage, which prevent blood flow to parts of the heart or brain. Schematic illustration of atherosclerosis is given in Figure 1.

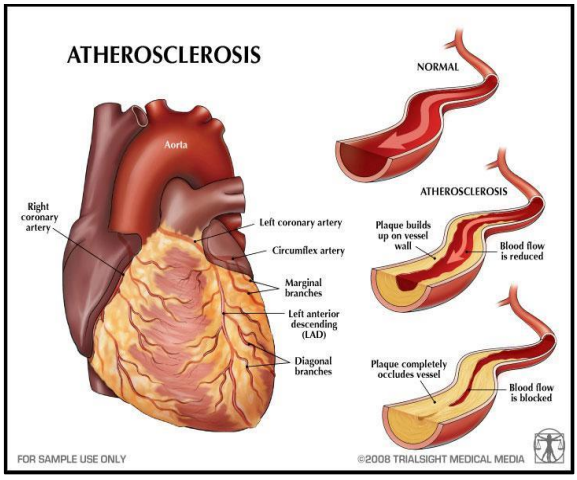

Figure 1. Schematic illustration of the development process of atherosclerosis. ©2008 TRIALSIGHT MEDIA

Atherosclerotic lesions most commonly occur within arteries, but these lesions are especially seen at vessels curves and bifurcations where smooth blood flow is disrupted by shear forces produced by blood flow (Winkel et al. 2015). Vascular endothelium, monocytes/macrophages, smooth muscle cells, some growth factors and cytokines are involved in the atherosclerotic process. It is now widely recognized that a systemic inflammatory process is involved in atherogenesis, causing vascular damage. Therefore, people with autoimmune diseases characterized by chronic systemic inflammation such as rheumatoid arthritis (RA) are at an increased risk of developing CVD.

1.2.Risk factors of CVDs

In general, risk factors of CVDs include but are not limited with smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, sedentary lifestyle and dietary factors (Capewell et al. 2010). The WHO reported that the incidence of CVDs can be reduced by half by the control of hypertension, obesity, cholesterol and smoking (WHO 2016). For a more accurate classification, risk factors of CVDs can be divided into two groups as modifiable and non-modifiable factors (Figure 2). Modifiable risk factors can be further divided into two groups as behavioral risk factors (tobacco use, unhealthy diet, sedentary life etc.) and physical risk factors (hypertension, high cholesterol, diabetes mellitus, obesity etc). On the other hand, several studies have shown the elevation of certain analytical parameters as physical risk factors of CVDs. These parameters include hsCRP, lipoprotein (a), fibrinogens, glycated hemoglobin and ceruloplasmin (Kumar et al. 2008). In addition, high homocysteine levels are associated with a higher risk of CVDs and stroke.

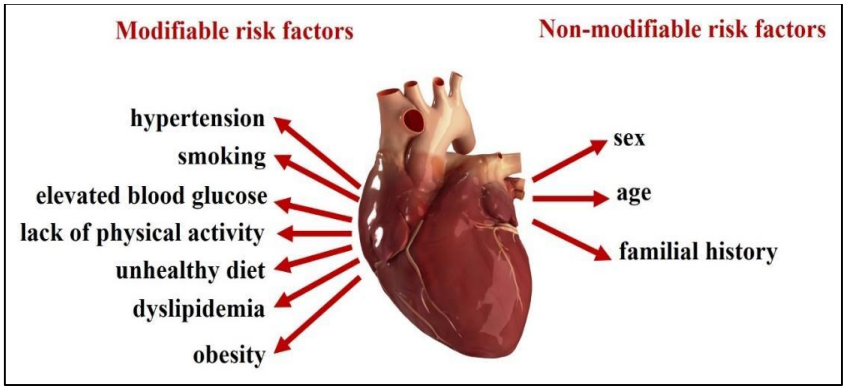

Figure 2. Risk factors of cardiovascular diseases.

1.3.How to prevent risk factors of CVDs

Most CVDs can be prevented by addressing behavioral risk factors. Lifestyle changes can be an important preventive measure in order to overcome the risk of developing CVDs. These changes may include at least 30 minutes of brisk walking 3-4 times a week, >4 servings/day of fresh fruits and vegetables etc. Grains and green leafy vegetables should be included in the diet. Tobacco use should be stopped and harmful alcohol consumption should be avoided. Being dependent on natural food instead of supplements could reduce the risk of future CVDs. People who are at a high risk of developing CVD due to modifiable physical risk factors such as hypertension, diabetes mellitus and hyperlipidemia need early

recognition of their conditions and management with appropriate medical therapy.

1..Symptoms of CVDs

Mostly a heart attack or stroke may be the underlying cause of CVDs. According to the data published by WHO, 85% of CVDs in 2016 resulted from a heart attack or stroke. These conditions are equal in men and women. The WHO estimates that 23.6 million people will die from CDV conditions by 2030 and mostly because of heart attack and stroke. Heart attack symptoms include (WHO 2017):

- Pain in the center of the chest
- Pain in the arms, left shoulder, jaw or back
- Shortness of breath, vomiting, cold sweat and becoming pale may also be observed.

Symptoms of a stroke are as follows (WHO 2017):

- Sudden onset of weakness and/or numbness in the face, arm. The weakness is mostly unilateral.
- Difficulty in speech, confusion
- Difficulty in vision
- Difficulty in walking and dizziness
- Fainting

2.Coronary Artery Disease

Also known as coronary heart disease or atherosclerotic heart disease, coronary artery disease (CAD) results from the inflammatory accumulation of macrophage white blood cells within the walls of the arteries supplying the myocardium. The lifetime risk of developing CAD after 40 years of age is 48% for men and 32% for women. Table 1 shows the major prognostic risk factors of coronary artery disease (Hachamovitch et al. 2003).

Table 1. Major prognostic risk parameters of coronary artery disease

Clinical features	Age Diabetes mellitus Hypertension Current smoking Prior MI, PVD Severity of angina	**Echocardiography**	LVEF < 50% Wall motion abnormality > 3
Laboratory markers	Total cholesterol hs CRP hs Troponin	**Stress Perfusion Scintigraphy**	Reversible perfusion defect > 10%LV
Exercise ECG	Exercise duration Duke treadmill score	**Coronary anatomy**	Left main disease 3-vessel disease especially proximal LAD Syntax score > 32

MI: Myocardial infarction LV: Left ventricle, PVD: Peripheral vascular disease HS: High

sensitivity LVEF: Left ventricle ejection fraction LAD: Left anterior descending artery.

CAD results from atherosclerosis of the coronaries or arteriosclerosis. In this process, the intima layer of the artery is damaged. Cholesterol begins to accumulate in the walls of the artery. One or several plaques adhere to the arterial endothelium, causing narrowing of the artery diameter, arterial occlusion and the formation of thrombosis. Mainly involved coronary arteries are the left coronary artery, left descending coronary artery, circumflex artery and right coronary artery (Figure 3).

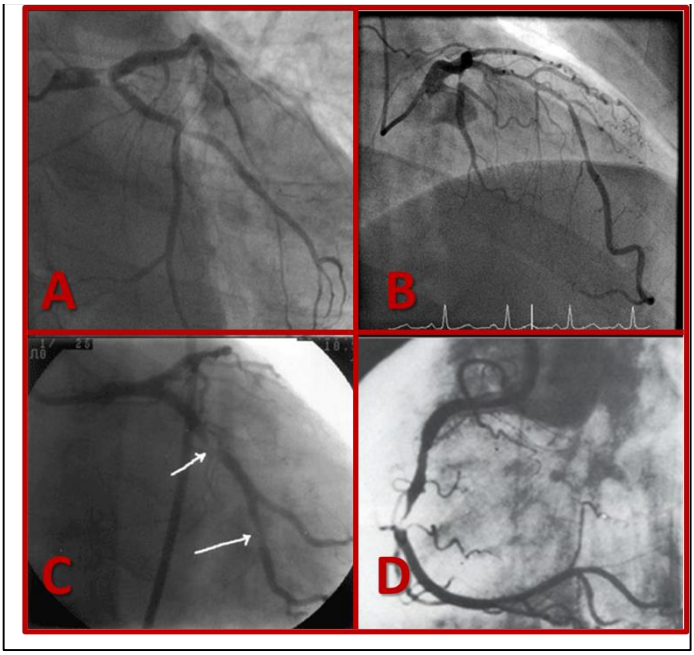

Figure 3. Mainly involved coronary arteries in atherosclerosis. **A.** Left coronary artery (LCA) disease. **B.** Left anterior descending (LAD) disease. **C.** Circumflex artery disease. **D.** Right coronary artery (RCA) disease.

2.1.Symptoms of CAD

The signs and symptoms of CAD are recognized at the advanced stage of the disease and most people do not show signs of the disease for years as the disease progresses and finally a sudden heart attack occurs. CAD is the most common cause of sudden death. The major symptom of CAD is chest pain, known as angina pectoris.

2.1.1.Angina Pectoris

Angina pectoris, which is one of the cardinal symptoms of CAD, was described for the first time by William Heberden in 1772 (Chapelle 1960). Almost half of CAD patients present with angina pectoris. Angina pectoris results from myocardial ischemia, which is caused by an impaired balance between the requirement and supply of myocardial O_2. Increased heart rate, contractility and wall tension increase the demand for oxygen. Coronary blood flow is provided by the pressure difference between diastolic blood pressure and end-diastolic blood pressure. Coronary occlusion or any other cause reducing coronary perfusion gradient will

result in myocardial ischemia. Angina pectoris manifests as a sensation of pressure in the chest, pain in the arm (usually one side), jaw and the other forms of discomfort. 'Discomfort' term is preferred over 'pain', because this sensation varies widely among individuals in intensity and character. People mostly do not perceive angina as pain unless it becomes severe.

Angina is divided into two subtypes as stable and unstable angina. The occurrence of stable angina is predictable. Stable angina occurs upon physical exertion or feeling considerable stress. Typically, the frequency of stable angina does not change and it does not become worse over time. On the contrary, unstable angina occurs at rest or on stress exertion. The frequency and severity of pain increase. An attack of unstable angina is an emergency and requires seeking medical aid. When left untreated; unstable angina leads to heart attack, heart failure or arrhythmias that can become life threatening conditions.

2.2.Diagnosis and treatment of CAD

The diagnosis of CAD is established through electrocardiogram (ECG), echocardiogram, exercise stress test, nuclear stress test, cardiac catheterization and angiogram, and cardiac CT scan. Treatment of CAD has three approaches including lifestyle changes, medical therapy and surgical therapy.

Lifestyle changes include quitting smoking, a healthy diet, regular exercise, weight loss and reducing stress. Medical therapy included administration of cholesterol modifying drugs, aspirin, beta-blockers, calcium channel blockers, ranolazine, nitroglycerin, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB). Surgical procedures aim to restore and/or improve coronary blood flow and include percutaneous coronary revascularization and coronary artery bypass grafting. Coronary artery bypass grafting (CABG) can be applied as cabg with heart lung pump, cabg in beating heart, aortic no tuch cabg, full arterialized cabg and minimally invasive cabg.

3.Hypertension

Hypertension is a chronic elevation of blood pressure that causes end-organ damage and leads to morbidity and mortality in the long term. It is a health condition occurring as a result of repeatedly elevated systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg. Systolic blood pressure is the pressure in the arteries as the heart pumps blood into the arteries, while diastolic blood pressure is the pressure that results from a relation of arteries after contraction (Cunha and Marks

2011). Systolic hypertension is a predictor of coronary and cerebrovascular risk especially in elderly patients. Treatment of systolic hypertension is effective in control of the risk and reducing morbidity in these patients. The pathogenesis of hypertension is a multifactorial and complex process. The kidney both contributes and is affected by hypertension (Hall JE et al. 2012). In hypertension, the extent of the target organs (heart, brain and kidneys) determines outcome.

Hypertension is a major health problem worldwide because of its high prevalence and association with cardiovascular diseases. Globally, hypertension causes 7.1 million premature deaths (Whitworth 2003). It has been estimated that 1.56 billion people will have hypertension by 2025 (Kearney et al. 2005). Hypertension is a common risk factor for many diseases including CVDs, cerebrovascular diseases and kidney disease, and is a major risk factor of premature mortality and morbidity worldwide (Limet al. 2013, Hay et al. 2017). Efficient management of hypertension has resulted in significant reduction of the incidences of coronary artery disease and stroke in developed countries. However, it remains a great concern to resolve in many regions of the world due to the increasing incidence of hypertension related diseases such as stroke, end-stage renal disease and heart failure (WHO 2004 hypertension report). Studies have reported that an individual who is normotensive at age 55 years has a 90% lifetime risk of developing hypertension within the rest of his/her life (Chobanian et al. 2003). Stages of hypertension is shown in Figure 4.

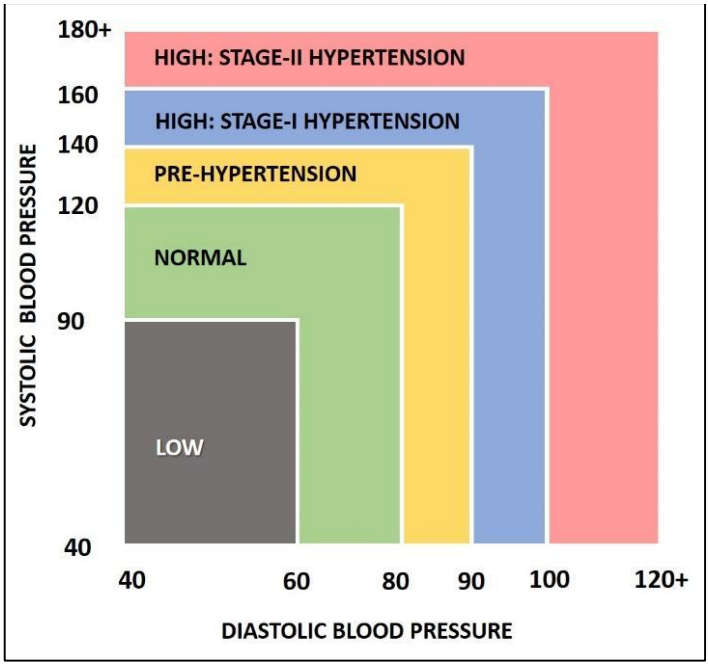

Figure 4. Staging of hypertension according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda (MD): National Heart, Lung, and Blood Institute (US) (JNC 2004).

3.1.Types of Hypertension

There are mainly two types of hypertension: primary (essential) and secondary hypertension. In primary hypertension, blood pressure increases, but the reason for this is not known and can cause cardiac, cerebral and renal damage. It is associated with some risk factors including ageing, genetic, and environmental factors (Weber et al. 2014, Messerli et al. 2007). Patients with primary hypertension have difficulty in memory and attention (Lande et al. 2017). The other type, secondary hypertension accounts for about 5% of all hypertension cases. The cause can be determined in this type of hypertension. Secondary hypertension is generally resulted from chronic renal disease, renal dysfunction, adrenal gland tumor etc. (Weber et al. 2014).

3.2.Risk factors of hypertension

The risk factors that can lead to hypertension include smoking, stress, excessive salt intake, obesity and alcohol. With tobacco exposure, the number of intracranial arterial segments increases with ahterosclerotic plaques, leading to hypertension (Gać P et al. 2017). Increased stress activates the sympathetic nervous system, increasing blood pressure

(Ziegler MG and M Milic 2017). Sympathetic system is also activated by salt intake because increased plasma volume and cardiac output due to salt intake. In people with essential hypertension, the most significant cause is obesity. Excessive alcohol intake causes hypertension through oxidative stress, vascular injury, decreased production of nitric oxide and impaired baroreceptors (Husain et al. 2014).

3.3.Complications of hypertension

Cardiac consequences of hypertension include CAD and left ventricular hypertrophy. CAD is associated with hypertension, which accelerates the disease, leading to myocardial ischemia and myocardial infarction. The incidence of myocardial incidence is higher in hypertensive patients. There are two major factors contributing to myocardial ischemia: (1) increased oxygen demand due to pressure and (2) decreased oxygen supply due to atheromatous lesions. Another complication of hypertension is heart failure that results from chronic pressure overload. Aortic aneurysms and dissections, which cause serious mortality due to hypertasion, may also develop. Treatment of aortic aneurysm dissection is usually surgical.

3.4.Treatment of hypertension

Lifestyle changes are the first step to control hypertension. These changes include sodium restriction, weight loss, decreasing alcohol intake and regular exercise. Medical therapy is indicated when lifestyle changes fail or hypertension is already at an advanced stage. All anti-hypertensive drugs exert their actions by decreasing cardiac output or peripheral vascular resistance or both. The most commonly used antihypertensive drugs are as follows:

- Diuretics
- Beta-blockers
- Calcium channel blockers
- Angiotensin converting enzyme inhibitors
- Angiotensin II receptor blockers
- α1-Adrenergic blockers
- Direct vasodilators
- Central adrenergic inhibitors
- Natriuretic peptides

5.Heart valve disease (Valvular heart disease)

Heart valve disease (HVD) is a group of the cardiac pathologies seen in one or more of the four valves of the heart, which progresses by ageing and leads to serious health problems if left untreated. The exact incidence of heart valve disease is unknown. Its prevalence in the USA has been

reported as 2.5% (Nkomo et al. 2006). Common forms of HVD are given in Figure 5. The most significant forms of HVD include aortic stenosis, aortic regurgitation (chronic and acute), mitral stenosis and mitral regurgitation (chronic and acute), and will be discussed below.

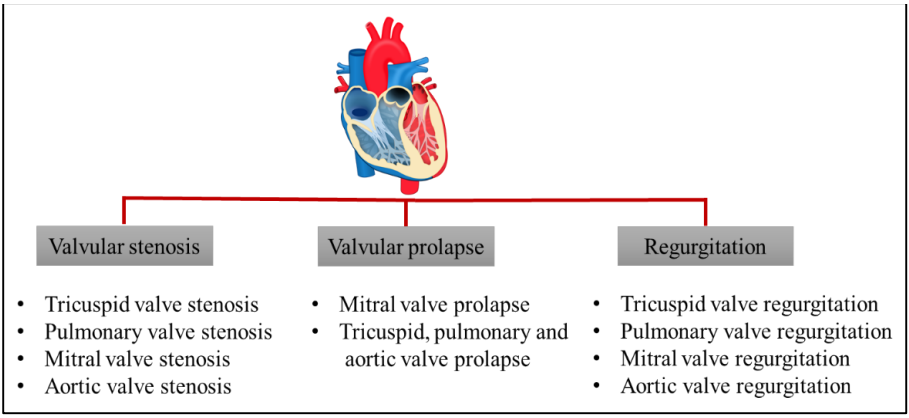

Figure 5. Common forms of heart valve disease

5.1.Aortic valve stenosis

Aortic stenosis (AS) is the most common valve disease characterized by progressive thickening, calcification and fibrosis of valvular leaflets, leading to valve obstruction (Pawade et al. 2015). AS is a public health problem and the most common form of HVD in Western countries as reported by a study, which has evaluated the effects of this valvular pathology in 185 countries (Yadgir et al. 2020). Its rate of prevalence is similar between men and women. Light alcohol consumption has been found to be associated with a low risk of AS, while smoking, hypertension, diabetes mellitus, renal insufficiency, obesity and metabolic syndrome seem to be involved in the development of AS (Larsson et al. 2017). Patients typically become symptomatic when the aortic valve area is severely reduced and show symptoms such as angina, dyspnea and fainting, usually upon exercise. AS is the second most common fatal heart disease following coronary artery disease. Three major causes of AS are atherosclerosis, congenitally malformed valves and rheumatic heart disease. Most people with AS do not show symptoms until the amount of restricted blood flow becomes significantly reduced. The main symptoms of AS include: angina, shortness of breath, dizziness, edematous ankles and/or feet and significantly decreased ability to perform daily activities.

The diagnosis of AS starts with physical examination. The classic crescendo-decrescendo murmur is heard especially at the right upper sternal border. In severe AS, the physical findings of systolic heart failure

becomes more prominent. After physical examination, the patient is evaluated with a transthoracic echocardiogram. Alternative diagnoses are ruled out with this examination. Echocardiographic examination also can detect associated aortic regurgitation, which can complicate the management of AS. (Nishimura et al. 2014). When non-invasive assessments of the aortic valve fail, the first invasive method to be attempted is catheterization. The management of AS included medical therapy and surgery. Medical management of patients with mild-to-moderate AS include ACE inhibitors, beta-blockers and aldosterone receptor antagonists. In addition, comorbidity in these patients such as hypertension should also be managed properly. Aortic balloon valvuloplasty is preferred in children, while surgical intervention may include mechanical/bioprosthetic valve replacement.

5.2.Aortic regurgitation

Aortic regurgitation is a disease characterized by inadequate closure of the valvular leaflets. AR occurs when part of the blood ejected from the left ventricle into the aorta during the systolic phase flows back to the left ventricle during the diastolic phase. The incidence of AR has been reported as 13%in men and 8.5% in women (Coffey et al. 2016). Based on the etiology, AR can be classified as acute and chronic AR and based on the severity as mild, moderate and severe AR. Because of this backflow, workload of the left ventricle increases. Patients with acute AR may remain asymptomatic for long years. However, if left unnoticed and untreated, this condition eventually may lead to congestive heart failure. In chronic AR, left ventricular hypertrophy enables the left ventricle to adapt to increased diastolic volume. Whereas in acute AR, there is no time for this adaption and the increase in the left ventricular diastolic volume results in o the increased left ventricular diastolic pressure (Stout and Verrier 2009).

As AR worsens, symptoms begin to manifest. The symptoms of AR include fatigue, weakness, dyspnea, angina, and arrhythmias. Echocardiography plays a critical role both in diagnosis and management of AR. In evaluation of patients with AR, classifying the severity of the regurgitation is the first step. A loud diastolic murmur, a third heart sound and a widened pulse pressure are signs of severe AR, but are not specific (Tribouilloy et al. 2001). ECG, chest X-ray and echocardiography are adjuvant imaging modalities. Doppler echocardiography is the mainstay of the evaluation of AR. In the management, AR patients may have a high risk of developing endocarditis and should be administered antibiotic prophylaxis. Conservative treatment usually contains vasodilators mostly in mild-to-moderate AR, while surgical option includes valve replacement using either a mechanical or a biological prosthesis in patients with severe AR.

5.3.Mitral stenosis

Mitral stenosis (MS) is a valvular heart disease characterized by inability of the blood to flow from the left atrium to the left ventricle at the level of the mitral valve. MS is divided into two classes as pure MS and mixed MS. Pure MS accounts for about 25% of all heart valve diseases, while this rate is nearly 40% in mixed MS. Chronic rheumatic heart disease, rheumatic fever, hypoplasia of the left ventricular cavity and endocardial fibroelastosis are involved in the etiology of MS. Among these, the most common cause of MS is rheumatic fever (Gordon et al. 1992).

Symptoms of MS include dyspnea, cough, tachycardia, fatigue, hoarseness, edema in feet and embolic symptoms. The diagnosis of MS is established with physical examination, ECG, exercise tolerance test, chest X-ray and echocardiography. Medical treatment of MS includes treatment of complications such as atrial fibrillation and dyspnea. The used medications include beta-blockers, calcium channel blockers, long-acting nitrates, warfarin and heparin (Nishimura et al. 2014, ESC 2012). Surgical treatment options include balloon and mitral valve replacement.

5.4.Mitral regurgitation

Mitral regurgitation (MR) is a valvular disease caused by pathology of the valve that prevents normal closure (primary MS) or LV dysfunction, which affects proper closure of the mitral valve (secondary MR). Based on the disease onset MR can be acute or chronic in nature. Acute MR results from any disruption of normal valvular mechanism. Possible pathologies in acute MR are as follows:

- Growth of vegetations on the leaflets in case of endocarditis.
- Chordae rupture in patients with degenerative disease.
- Papillary muscle rupture because of an ST-elevation MI.

In chronic MR, anatomy of the mitral valve is normal, but its function is impaired due to left ventricular pathologies such as inability of the leaflets to meet properly due to dilatation of mitral annulus, and abnormal movement of the left ventricle following infarction or ischemia. MR (acute and chronic forms) affects approximately 5/10,000 people.

Symptoms of MR include dyspnea with exertion, fatigue, reduced exercise ability, tachycardia and swelling of the legs, abdomen and veins in the neck. Chest pain is less common. Before the treatment, severity of MR should be established. Imaging tools used to classify severity of MR include transoesophageal echocardiography and transthoracic echocardiography. In addition, ECG, exercise test and biochemical analysis are also performed. Medical treatment of primary MR consists of

vasodilators and inotropic agents. Whereas, in chronic MR classical heart failure treatment is applied with beta-blockers, ACE inhibitors, aldosterone antagonists and diuretics. In surgical treatment, valve repair is preferred over replacement as much as possible (Feldman et al. 2011).

6.Peripheral artery disease

Peripheral artery disease (PAD) is an acute/chronic disease occurring in the arteries that provide blood flow from the aorta toward the periphery in the body. PAD is narrowing of the peripheral arteries supplying the legs, arms, stomach and head. PAD is caused by atherosclerosis and most commonly affects arteries in the legs. PAD patients are at a very high risk of developing cardiac or cerebrovascular disease (Shammas 2007). Risk factors of PAD include:

- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Homocysteinemia
- Uric acid metabolism
- Hypercoagulation
- Smoking
- Obesity
- CAD

PAD has serious complications including critical limb ischemia, stroke and heart attack. Symptoms of PAD are painful activities such as climbing stairs, intermittent claudication, numbness and weakness of the legs, coldness in one leg compared to other, color change in legs, slower growth of toenails, ischemic ulcer, a weak pulse in the legs or feet and erectile dysfunction in men.

Findings on physical examinations include inability to receive pulses, heat differences between the extremities, muscle atrophies and ischemic color changes in the extremities. Management of PAD involves lifestyle changes, medical treatment (iloprost, clopidogrel, cilostazol, acetyl salic acid), intravascular interventions and surgical interventions (anatomic and/or extra-anatomic bypass procedures). The measures that should be taken to prevent PAD are:

- Quitting smoking
- Keeping blood glucose under control
- Regular exercise

- Lowering cholesterol and blood pressure
- Low-saturated fat diet
- Weight loss for overweight or obese persons

6.1.Acute extremity ischemia (Acute limb ischemia)

Acute extremity ischemia (AEI) is a condition in which localized ischemia develops as a result of the occlusion of arterial structure by an embolic or thrombotic material. AEI is a sudden decrease in limb perfusion, which leads to a threat in the viability of the affected limb (Setghi et al. 2013). The most common complaint is sudden-onset pain and coldness in the affected extremity. Embolism, thrombosis, hypercoagulability states, arterial trauma, iatrogenic causes, aortic dissection, vasospasm, arteritides and thoracic outlet syndrome are involved in the etiology of AEI. Findings in the physical examination are shown in Figure 6.

Figure 6. Findings of acute extremity ischemia

Differential diagnosis of AEI involves critical chronic extremity ischemia, acute deep vein thrombosis, spinal cord or peripheral nerve compression. The diagnosis of AEI is established with medical history, physical examination, biochemical analysis (including lactate and thrombophilia screening), ECG, Doppler ultrasound scan and CT angiography (Van DH et al. 2018). Conservative management of AEI is carried out with a prolonged course of heparin and regular assessment of the patient, although AEI is a surgical emergency. Surgical treatment options of embolic-cause AEI are embolectomy with a Fogarty catheter, local intra-arterial thrombolysis and bypass surgery in the case of insufficient flow back, while thrombotic AEI is treated with local intra-arterial thrombolysis, angioplasty and bypass surgery (Fluck et al. 2020).

7.Venous disorders

Common venous system disorders include chronic venous insufficiency, deep vein thrombosis, excessive blood clotting, superficial venous thrombosis (phlebitis) and varicose. Venous disease is more common than PAD and affects about 30 million people only in the USA (Criqui and Aboyans 2015).

Symptoms of venous disorders involve burning, fatigue, itching, pain, swelling, throbbing, muscle cramping, pigmentation and ulcer depending on the type of the disease. CEAP classification is used for standardization of venous disorders. CEAP includes a description of the clinical class (C) based on the etiology (E), anatomical (A) distribution of the reflux or obstruction in the veins and underlying pathophysiology (reflux or obstruction) (P). CEAP classification of venous disorders is shown in Table 2 (Eklof et al. 2004).

Table 2. CEAP classification of venous disorders

CEAP	Clinical Classification
C0	No visible or palpable sign of venous disease
C1	Telangiectasies or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis
C5	Healed venous ulcer
C6	Active venous ulcer

Age, gender, weight height, bowel habits, a history of deep venous thrombosis and genetics, sedentary life and occupation predispose to develop varicose veins (Pfisterer et al. 2014). Treatment of venous disorder includes several techniques such as compression therapy, endovenous laser ablation, radiofrequency ablation, endothermal heat-induced thrombosis.

Non-thermal treatment options are sclerotherapy, mechanochemical ablation, and cyanoacrylate.

8.Deep vein thrombosis (DVT)

DVT and its major complication pulmonary embolism, together known as venous thromboembolism (VTE) are one of the important causes of morbidity and mortality worldwide. VTE is the third most common cardiovascular pathology (Raskob 2014). In the USA, 900,000 new cases and 300,000 deaths are reported annually due to VTE (Heit 2017). DVT usually develops in the deep veins of the legs, leading to pain, edema, redness and abnormalities in gait. The development of DVT involves a complex cascade of events. When limb muscles do not contract properly and regularly, blood flow rate decreases in certain veins, increasing the risk for developing DVT (Bovill and van der Vliet 2011). Risk factors of DVT involve recent surgery, recent trauma to the leg, pregnancy, immobilization due to a condition such as a medical illness, hormonal medications including contraceptives and genetic factors.

Diagnosis of DVT is based on imaging studies including duplex ultrasonography, D-dimer blood test, contrast venography and magnetic resonance imaging. Medical treatment of DVT is applied with anticoagulants, thrombolytics. Compression therapy with stockings and compression devices. Thrombectomy is used as the surgical approach in the treatment of DVT. Interventional radiology procedures are also used for the treatment of DVT. Mechanical thrombectomy is used following interventional radiologic procedures in selected patients with acute DVT, while balloon angioplasty and stent placement can be used in patients with chronic DVT.

9.Cerebrovascular disease

Cerebrovascular disease is a group of conditions and disorders that affect blood vessels and blood supply to the brain. The most common cause of cerebrovascular disease is atherosclerosis. In addition, thrombosis and cerebral venous thrombosis may also cause cerebrovascular disease. Cerebrovascular disease is the fifth most common cause of mortality in the USA with 147.810 deaths in 2018 (CDC 2018). Common types of cerebrovascular diseases are shown in Figure 7.

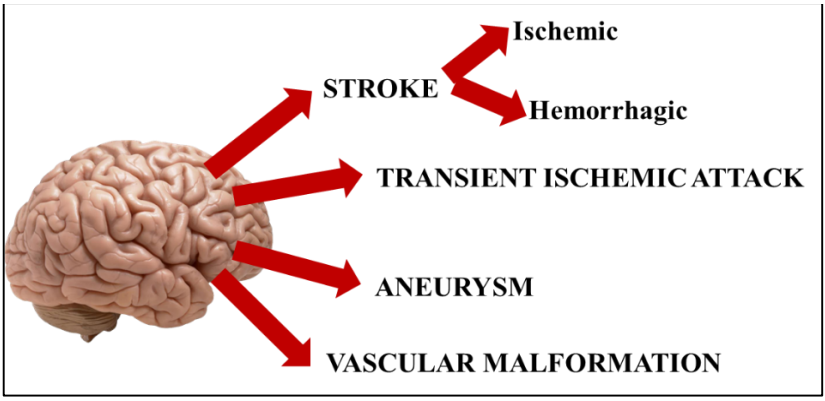

Figure 7. Cerebrovascular diseases

Although symptoms of cerebrovascular disease vary depending on the site of the blockage, the common symptoms include a severe and sudden-onset headache, hemiplegia, confusion, hemiparesis and slurred speech. The most common cerebrovascular disease is by far stroke.

Stroke is a cerebrovascular disease characterized by sudden-onset neurologic deficit mostly due to brain infarction (ischemic stroke) and rarely because of intracerebral hemorrhage (Johnston et al. 2009). Stroke also significantly contributes to the development of cognitive decline and dementia (Viswanathan et al. 2009). Stroke causes significant morbidity and mortality as well as healthcare costs worldwide. There is also a considerable burden of post-stroke care (Rajsic et al. 2018).

Common factors leading to stroke are large artery atheroma and cardiac embolism sources in ischemic stroke, while small artery disease is involved both in ischemic and hemorrhagic stroke (Greenberg 2006).

Risk factors of stroke include age, race, waist-to-hip ratio, family history, smoking, alcohol consumption, hypertension, diabetes mellitus hyperlipidemia, atrial fibrillation, Western style diets (O'Donnell 2010) and obesity. Signs and symptoms of stroke are as follows (CDC 2020):

- Sudden numbness or weakness in the face, arms or legs (especially unilateral)
- Sudden difficulty in speaking and understanding, confusion
- Sudden problem in seeing by one eye or both eyes
- Sudden trouble in walking, dizziness, loss of balance, impaired gait
- Sudden-onset headache of unknown cause

Stroke prevention is achieved by modifying the risk factors. The best preventive measures to be taken against stroke are eating a healthy diet, avoiding smoking and alcohol abuse, and regular exercise.

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CHAPTER IV

ABBREVIATED BREAST MRI PROTOCOLS IN BREAST CANCER SCREENING- REVIEW ARTICLE

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1.Introduction

Breast cancer is the second fatal cancer after lung cancer in women (1). Mammography (MG) is currently the most effective method used in breast cancer screening (2). However, breast cancer is still one of the most important health problems, despite mammographic screening programs and technical advances in mammography for more than 30 years. Studies have shown lower sensitivity of mammography which is about 70-85% (2,3). The most important reasons of the low sensitivity of mammography are dense breast structure, and inability to detect biologically aggressive tumors (4). A screening program should have as much as possible contributing to the patient survival and ability to detecting biologically important tumors. Most of the criticisms made about mammography on breast cancer screening are on these topics (5). Several imaging modalities used in detecting the breast cancer in daily practice sech as digital breast tomosynthesis (DBT), ultrasound (US), and magnetic resonance imaging (MRI). DBT was predicted to be beneficial particularly in dense breasts however, the contribution was less than expected with an average 1.2 per 1000 patients (6). Ultrasonography, and fully automatic breast US are useful in the diagnosis of breast cancer in women with dense breast structure, however the limitations are longer examination time, lower sensitivity, and higher rates of unnecessary biopsies (7). Moreover, the detection rate of additional cancer is moderate as many published studies have shown the rate as approximately 2–4.4/1000 in examined women (7-9). Breast MRI has been shown to be the most sensitive imaging modality for the detection of breast cancer (both invasive, and ductal carcinoma in situ) (10-12). MRI is not effected by breast density as MG, and relies on contrast enhancement, so can detect more biologically relevant cancers due to angiogenic activity (4). Due to these advantages, MRI is used as a standard method with MG in screening high-risk patients.

The standard full diagnostic protocol (FDP) of breast MRI consists of multiple sequences before and after contrast enhancement with and without fat suppression with examination time ranging from 20-60 minutes. The abbreviated protocols (AP) reduce the interpretation time of the images, and the cost due to shorter imaging time (11). Therefore, AP breast MRI has recently been investigated as a supplemental screening method for women in high and average risk groups.

In the present review the different AP breast MRI protocols used for screening in high and average risk of breast cancer, and the superiority and limitations of the procedure will be studied, and future possible application areas will be discussed.

2.Literature Review

Kuhl and colleagues were the first group who explored the use of AP breast MRI in 2014 (12). They investigated whether AP was suitable for breast MRI screening, and compared the procedure with FDP. 443 women at mild to moderately increased risk of breast cancer, and 606 screening MRI examinations were evaluated in the study. AP consisted of a single pre-contrast, first post-contrast T1 weighted sequence with the substracted and a single maximum-intensity projection (MIP) images. First, the MIP images were evaluated for significant contrast enhancement by two experienced and blinded radiologists. Then, the substracted images, and FDP were evaluated, and the evaluation time of each section was separately noted. Similar rate of cancer detection, similar sensitivity, specificity and PPV were found with the AP for screening of women with dense breast. This study showed that MRI acquisition time (3 min versus 17 min), and interpretation time (28 sec versus 2-4 min) might be substantially reduced with the AP without affecting the cancer yield, and the diagnostic accuracy.

In 2015, Mango et al. published a study which investigated whether so many sequences were needed to detect breast cancer (13). MRI images of 100 breast cancer patients were retrospectively evaluated by four radiologists. The AP consisted of only one pre-contrast and one post-contrast T1 weighted sequence. Post-processed subtracted first post-contrast and subtraction maximum intensity projection images were also obtained. They found no significant difference between the sensitivities within each sequence among four readers.

Heacock et al. evaluated the efficacy of the T2-weighted sequence added to AP in a study published in 2016 that included 107 patients who were retrospectively diagnosed with breast cancer (14). AP included the pre-contrast, and post-contrast T1 weighted sequences with subtracted images. Three breast radiologists separately evaluated the images. Protocols designed into 3 groups as AP1; T1-weighted non-contrast, post-

contrast and post-contrast subtracted images, AP2; T1-weighted images with clinical history and prior imaging, and AP3; T1-weighted images and T2-weighted images with clinical history and prior imaging. Cancer detection percentages were 97.8%, 99.4%, and 99.4%, respectively. This study showed that the addition of T2 sequence provided no statistically significant difference however, increased the lesion visibility.

Grimm et al. published another feasibility study to compare the performance of two different AP (AP-1 and AP-2), and FDP for breast cancer screening in the high-risk group (15). They retrospectively evaluated forty-eight breast MRIs [24 normal, 12 benign, and 12 malignant (8 IDC, 1 ILC, and 3 DCIS)]. The period between the short and long protocol evaluation was one month, and 3 experienced radiologists performed the evaluation. AP-1 included fat saturated pre-contrast T2-weighted, pre-contrast T1-weighted, and first pass T1-weighted post-contrast sequences and AP-2 included the abbreviated 1 protocol plus the second pass T1-weighted post-contrast sequence. There was no statistically significant difference between sensitivity, and specificity of FDP, AP-1, and AP-2. Overall sensitivity was 86% for AP 1, 89% for AP 2, and 95% for FDP. The specificity of AP 1 was 52%, AP 2 was 45%, and FDP was 52%. This study showed the average image interpretation time for AP 1 was 2.98±1.86 for FDP, and 2.95 ± 1.5 minutes. The results of this study demonstrated that the use of AP breast MRI for breast cancer screening can be a cost-effective method due to shorter examination and interpretation time (15).

In 2016, Harvey and colleagues published a study in which 568 high-risk patients were screened (16). In this study, they evaluated the AP and FDP. AP consisted of only pre-contrast and first post-contrast fat-suppressed T1 sequences subsequently, and the MIP and subtraction images were obtained. The mean scan time for AP was 4.4 minutes, and 23.2 minutes for FDP. Interpretation times were 1.55 for AP, and 6.43 minutes for FDP. Only 12 (2.1%) cases required additional MRI evaluation. Seven cancers were detected in this study (5 were invasive, and 2 were in situ ductal carcinoma), all diagnosed cancers were identified in both protocols. Their study showed statistically significant differences between scanning, and the interpretation times. The study also showed that AP was equally effective as FDP in cancer detection in high risk patients (16).

In 2017, Panigrahi and colleagues published a prospective cohort study including 1052 high-risk MRI cases (17). This study investigated the effectiveness of AP in breast cancer screening and its concordance with the Breast Imaging Reporting and Data System (BI-RADS) classification. The abbreviated protocol included a pre-contrast T1-weighted sequence with fat saturation, and a single post-contrast T1-weighted sequence with

fat saturation. Fourteen cancers were detected, and all cancers were diagnosed with both AP, and FDP. Changes in BI-RADS category were detected in only 3.4% of cases after FDP assessment.

Chen et al. included 356 women who had dense breast tissue with negative mammography findings into their study published in Korea in 2017 (18). MRI images were retrospectively divided into 3 groups (AP-1, AP-2, and FDP). As in previous studies, AP-1 consisted of a pre-contrast and a post-contrast T1-weighted series with subtracted and MIP images while AP-2 consisted of diffusion weighted imaging (DWI) series in addition to AP-1. Average interpretation times with the AP-1, AP-2, FDP were 37 seconds, 54 seconds and 3 minutes respectively, and there was a statistically significant difference between AP, and FDP. Fourteen cancers were detected. There were no significant differences in sensitivity among AP-1, AP-2, and FDP in the diagnosis of breast cancer. However, the specificity of AP-1 was significantly lower than that of AP-2 and FDP and there was no difference between AP-2, and FDP. Researchers in that study found that adding DWI to AP in screening of dense breast structure was as effective as FDP in detecting cancer, and at the same time effective in reducing the cost (18).

Petrillo et al. published a retrospective study evaluating 508 patients with MR images in 2017 (19). Abbreviated protocol included one pre-contrast, and the first post-contrast T1-weighted series. Full protocol consisted of four post-contrast, and one pre-contrast T1-weighted series. 206 out of 207 cancers were diagnosed by both FDP, and AP. There was not statistically significant difference between the performances of these two protocols (19).

Dogan and her colleagues evaluated 23 high-risk women by AP and FDP breast MRI in a feasibility study published by the American College of Radiology in 2018 (20). The AP included a single T2W fast spin-echo, triple echo Dixon T2 sequence, and a 3D dual-echo fast spoiled gradient-echo two-point Dixon sequence for volumetric T1W imaging prior to and after contrast as the dynamic sequence. FDP included unenhanced T1-weighted axial and sagittal, dynamic contrast-enhanced T1-weighted gradient-echo sequence, iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) and DWI sequences. The mean acquisition time for AP was 9.42 minutes, and 22.09 minutes for FDP. These results showed that AP consisting of high resolution T2-weighted imaging, unenhanced T1-weighted imaging, and four phases of contrast-enhanced T1-weighted imaging had significantly shorter acquisition time compared with the time in FDP. In addition, they found no statistical differences on image quality, and in detecting anatomical details between two protocols.

Oldrini et al. aimed to compare the diagnostic performance, and interpretation time of two protocols in 2018 (21). They retrospectively evaluated 90 breast MR examinations (30 were BI-RADS 1-2, 30 were BI-RADS 3, 30 were BI-RADS 4-5). Their study showed that using the abbreviated protocol decreased the interpretation time with no difference in sensitivity, and specificity. There was a high degree of consortium between AP, and FDP.

Choi et al. investigated the effectiveness of AP including fat-suppressed T2-weighted imaging, pre- and post-contrast T1-weighted, and subtracted MIP images for the screening of women with a history of breast cancer surgery in a study published in 2018 (22). They prospectively included 725 women who had a previous history of breast cancer history into the study. They found twelve cancers (7 cancers could not be diagnosed with second look US, and MG while 5 cancers could be diagnosed with second look US, and MG). This study has shown that AP is an effective method in screening of patients with a history of breast cancer in terms of both early detection of cancer, and diagnosis of possible cancer in the contralateral breast.

Yamada et al. investigated the detectability of breast cancer with unenhanced, and enhanced AP MRI in their study published in Japan in 2018 (23). Unenhanced AP (AP1) included fat-supressed T2 weighted images, DWI and MIP which were derived from DWI. Enhanced AP (AP2) included fat-supressed T2 weighted images, second post contrast T1-weighted squences and MIP derived from post-contrast images. Eighty-seven patients with 89 breast cancer lesions $\leq$ 2 cm in diameter were included into the study. The images were retrospectively evaluated by two radiologists. The sensitivity/specificity for AP1 and AP2 for reader 1 was 89.9/97.6% and 95.5/90.6%, for reader 2 was 95.5/94.1% and 98.9/94.1%, respectively. In this study, researchers concluded that the unenhanced AP with DWI may compete with the enhanced AP in the evaluation of cases known to have breast cancer below 2 cm in diameter.

3.Considerations

The initiation of breast cancer screening in 1970s enabled a great deal of knowledge on breast cancer. Currently, breast cancer is known to have a heterogeneous genetic background, and the radiological appearance of each cancer with different genetic characteristics is different from each other. To give an example, the spiculations are a typical feature of luminal-A cancers (24,25). The cause of architectural distortion is desmoplastic reaction due to hypoxia of tumoral area (26). Necrosis resulted with microcalcifications (27,28). The investigation of the tumors that could be detected by mammography showed that approximately 90% are less aggressive tumors (29). Unfortunately, these characteristics are not usually

detected in rapidly growing and biologically important interval cancers. The examination of the breast structure characteristics of the screened population showed that almost half of the population has dense breast structure, which reduced the sensitivity of mammography to 30% (30). Besides, interval cancer rate should be equal to zero in an ideal screening method. However, the interval screening was reported to be 30-50% in mammography studies in Europe based screening studies (31).

Breast cancer is a type of cancer that can be screened because the patient can be diagnosed in the asymptomatic period, and the target population is specific. The starting of the routine mammographic screening of the target population is at age 40 in the United States, and at age 50 in Europe, and screening is performed in every 1-2 years (4). The most important features of the screening method are being easily accessible, fast and reliable. Today MG is used in screening because it is easily accessible, cost-effective and fast. However, the modern clinical approach requires the high sensitivity in screening method, in biologically aggressive tumors and low rate of interval cancer. Scientists who have struggled to find a solution to this problem have performed considerable studies particularly on AP breast MRI in recent years. Breast MRI is a diagnostic method which was used in the early 1990s (32-34). Multiple studies have shown that breast MRI had high diagnostic efficacy in various benign and malignant breast diseases regardless of breast density, tumor stage, and histopathological background (4). At present, screening breast MRI is used only in patients with a lifetime risk greater than 20% in accordance with the ACR guideline (35). This group especially includes BRCA positive patients. The investigation of the tumor characteristics of these patients showed that they were more aggressive, and mostly interval and was difficult to detect with mammography. Although the interval cancer rates decreased to zero by MRI, and MG screening has many disadvantages, the use of screening breast MRI is still unclear in the low, and average risk group in the literature (4,36).

The abbreviated protocol which is defined for further introduction of screening into daily practice, does not contain as many sequences as conventional MRI. The commonly used sequences in the studies in the literature were fat sat pre-contrast T1, and first post-contrast T1 sequences. The subtracted, and MIP examinations performed by post-processing were also added to these sequences (Table-1).

Table 1. Abbreviated Breast MRI Protocols Used in Twelve Studies

Study	T1 Pre-CE	T1 Post-CE First Pass	Substraction	MIP	T1 Post-CE Second Pass	T1 Post-CE Third Pass	T2	STIR	DWI
Kuhl et al., 2014	×	×	×	×					
Mango et al. 2015	×	×	×	×					
Heacock et al. 2016 AP 1	×	×	×	×					
Heacock et al. 2016 AP 2	×	×	×	×			×		
Grimm et al. 2015 AP 1	×	×	×				×		
Grimm et al. 2015 AP 2	×	×	×		×		×		
Harvey et al. 2016	×	×	×	×					
Dogan et al. 2018							Dixon T2 sequence and 3D dual-echo, fast spoiled gradient-echo two-point dixon sequence		

Chen et al. 2017 AP 1	×	×	×	×					
Chen et al. 2017 AP 2	×	×	×	×					×
Oldrini et al. 2018	×	×	×						
Choi et al. 2017	×	×	×	×			×		
Yamada et al. 2018 AP1				×					×
Yamada et al. 2018 AP2				×	×		×		
Panigrahi et al 2017	×	×	×	×					
Petrillo et al. 2017	×	×	×						

Different than FDP, kinetic examination cannot be performed, and only the early contrast enhancement of the lesion can be evaluated. In fact, the researchers demonstrated that a rapid wash-in is correlated with tumor grade, and invasive disease because the contrast between the angiogenic tumor, and the adjacent fibroglandular tissue was in the highest level at that moment (37). Grimm and colleagues added a second post-contrast sequence to AP while investigating the contribution of kinetic analysis and found no differences in reader sensitivity or specificity (15). Moreover, early contrast enhanced series were the eliminating background parenchymal enhancement (BPE) of normal fibroglandular tissue that can be seen in further contrast enhanced images.

Studies have shown that MRI acquisition time, and evaluation time of the images are significantly reduced with AP when compared with FDP owing to the decreased number of sequences to review. The shortest times

were reported as 3 minutes for acquisition time, and as 2.8 seconds for evaluation time (with MIP images only) in the study of Kuhl (12). The duration was only 4.4 minutes in the study of Dogan et al. in the full protocol implemented with fast sequences (20). (Table-2).

Table 2. Studies and pathology information.

References	**Number of patients**	**MRI examinations**	**Number of invasive carcinomas**	**Number of DCIS**	**Duration (FDP/AP/ minutes)**
Kuhl et al.	443	606	7	4	3
Mango et al.	100	100	79	21	15
Heacock et al.	107	107	94	13	12
Grimm et al.	48	48	9	3	11/13
Harvey et al.	505	568	5	2	4.4
Dogan et al.	23	23	0	0	9.42/22.09
Chen et al.	356	356	14		3
Oldrini et al.	90	90	25	1	-
Choi et al.	725	799	7	5	8.38
Yamada et al.	87	87	67	12	-
Panigrahi et al.	746	1056	14	2	3
Petrillo et al.	508	508	183	24	-

Figure 1, 2 and 3 show three cases in which the first, and second post-contrast images, DWI, MIP images were evaluated (Figure 1,2,3).

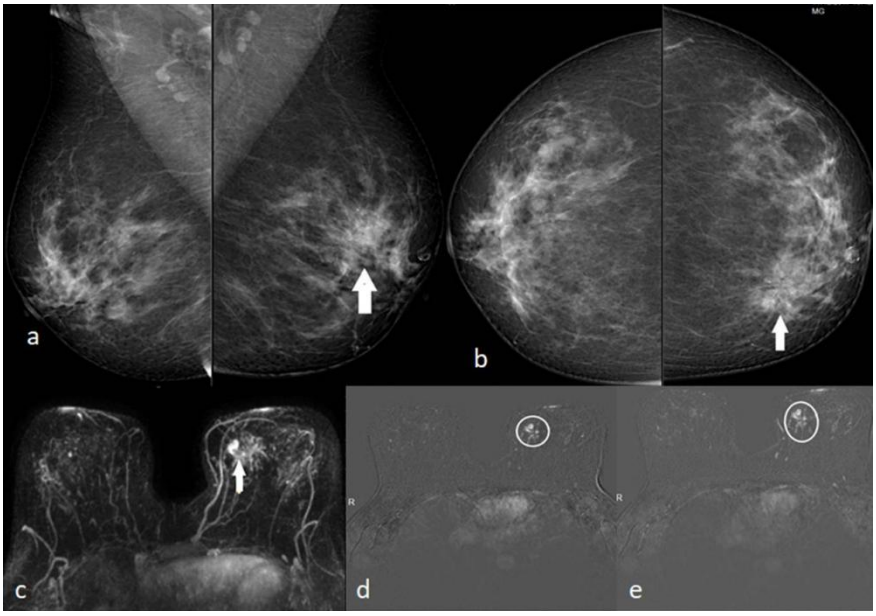

Figure 1. The patient aged 41 years diagnosed with invasive lobular carcinoma presented by mammography, and abbreviated MRI images. **a-b)** CC (craniocaudal) and MLO (medio-lateral-oblique) mammograms show parenchymal distortion with pleomorphic microcalcifications (arrows). **c)** MIP(Maximum Intesity Projection) image shows malignant lesion with greater contrast enhancement than adjacent normal parenchyma in the same area (arrow head) **d-e)** First and second post-contrast T1-weighted sequences with fat saturation show malignant lesion with irregular margins showing contrast enhancement, respectively (circles)**.**

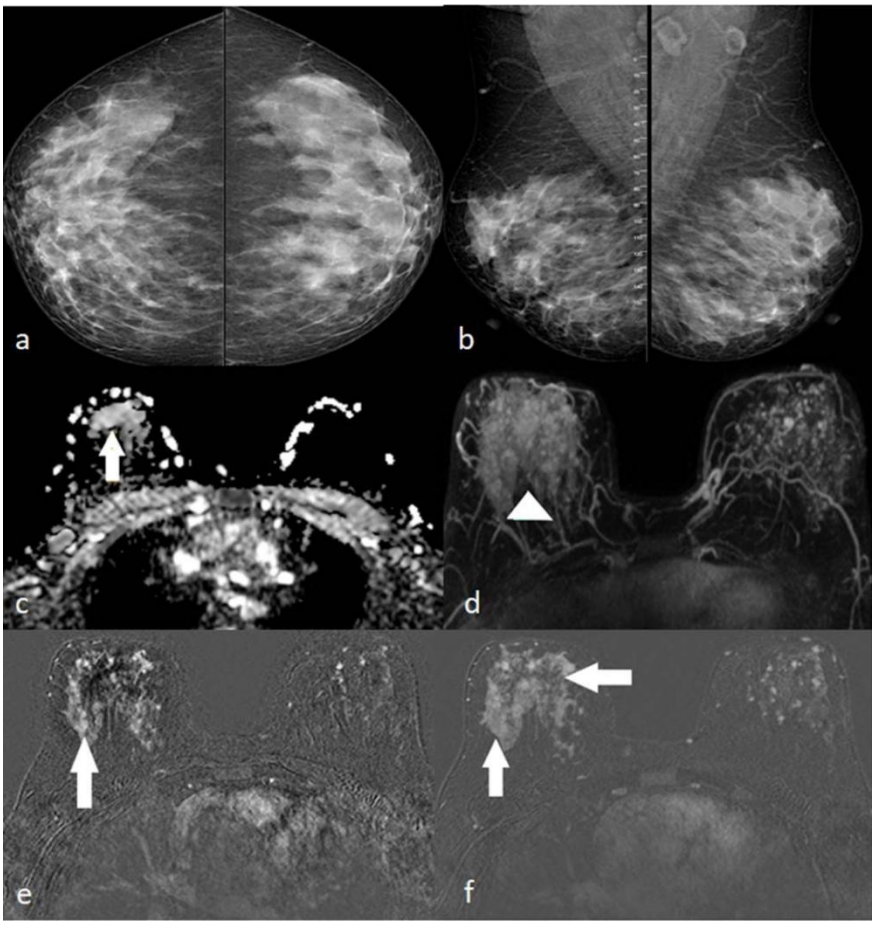

Figure 2. The patient aged 39 years presented with a palpaple mass in her right breast that was diagnosed with invasive tubular, and micropapillary carcinoma assosiated with in situ component. **a-b)** CC (craniocaudal) and MLO (medio-lateral-oblique) mammograms cannot show the lesion due to dense breast parenchyma structure**. c)** ADC (Apparent Diffusion Correlation) map image shows hypointensity due to the hypercellularity of the lesion (arrows). **d)** MIP (Maximum Intesity Projection) image shows infiltrative lesion with a wide area of contrast enhancement, without a clear mass configuration. **e-f)** First and second post-contrast T1-weighted sequences with fat saturation show the same infiltrative lesion with a wide area of contrast enhancement, without a clear mass configuration, respectively (arrows).

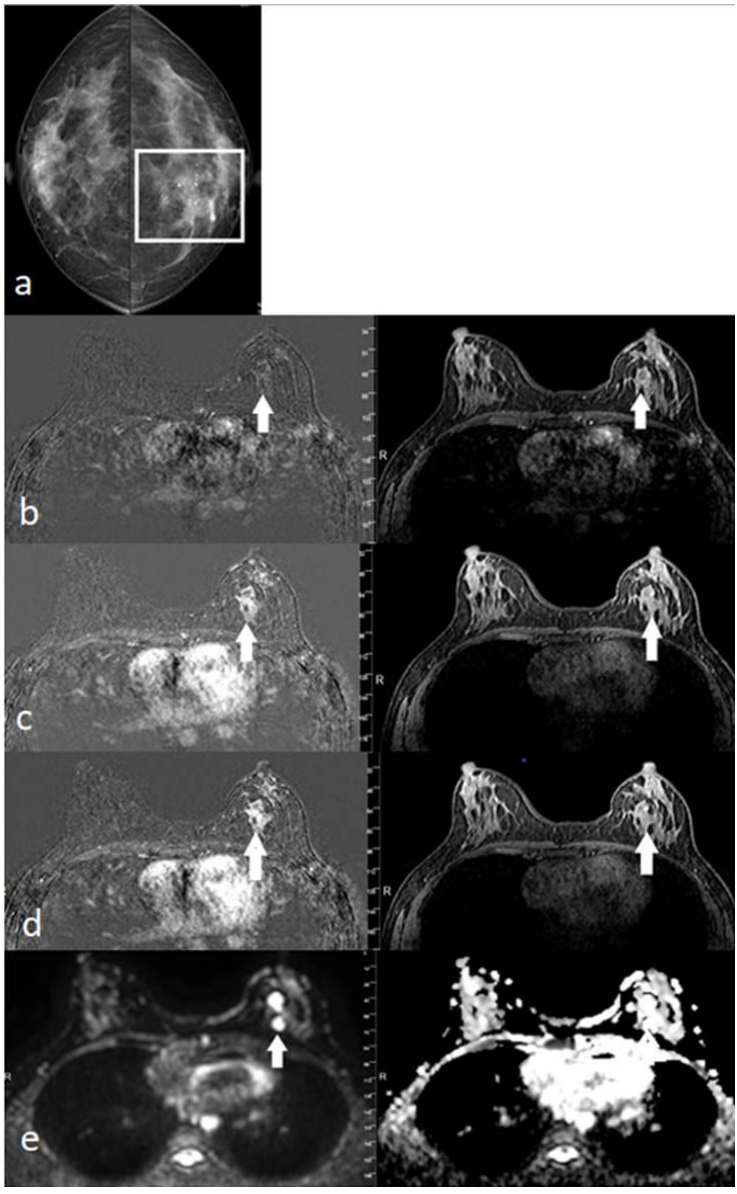

Figure 3. The patient aged 37 years diagnosed with a palpable mass in her left breast which was confirmed as mucinous carcinoma presented by mammography, and abbreviated MRI images. **a)** CC (craniocaudal) mammograms show malignant lesion with spiculated margins and amorphous microcalcifications in the inner quadrant of the left breast (square). **b-c-d)** The first, second and last post contrast subtracted, and nonsubtracted T1-weighted sequences images show a malignant lesion with peripherally contrast enhancement assosiated partly necrotic component (circles). **e)** DWI, and ADC (Apparent Diffusion Correlation) maps both show hyperintense lesion due to its hypocellularity, a general feature of mucinous carcinomas.

Although the use of different sequences, different patient numbers and populations, AP had the same cancer detection rates and diagnostic efficacy as FDP in nearly all published studies (Table-3). Dogan et al. used T2W fast spin-echo, triple echo Dixon T2 sequence, and a 3D dual-echo fast spoiled gradient-echo two-point Dixon sequence for volumetric T1W imaging before and after the contrast as the dynamic sequence in AP (20). The aim of their study was to determine anatomic detail as well as FDP, and to perform the kinetic analysis. Therefore, the MRI acquisition time could be reduced from 22 minutes to only 9.42 minutes. The difference of this study from other studies was the ability to perform the similar kinetic analysis.

Table 3. Sensitivity and Specificity of FDP vs. AP

	Sensitivity (%)		Specificity (%)	
Studies	**FDP**	**AP**	**FDP**	**AP**
Kuhl et al.	100	100, 90.9[a]	93.9	94.3
Mango et al.	n/a	96, 93[a]	n/a	n/a
Heacock et al.	n/a	97.8[b],99.4[c],99.4[d]	n/a	n /a
Grimm et al AP 1	95	86	52	52
Grimm et al.AP 2	95	89	52	45
Harvey et al.	n/a	100	n/a	n/a
Dogan et al.	n/a	n/a	n/a	n/a
Chen et al. AP 1	100	92.9	96.8	86.5
Chen et al. AP 2	100	100	96.8	95
Oldrini et al.	100[e] 100[f]	100[e] 100[f]	91.5[e] 94.4[f]	91.5[e] 95.1[f]
Choi et al.	n/a	100	n/a	89.2
Yamada et al.AP1	n/a	89.9[g]/95.5[h]	n/a	97.6[g]/94.1[h]
Yamada et al.AP2	n/a	95.5[g]/98.9[h]	n/a	90.6[g]/94.1[h]
Panigrahi et al.	81.8	81.8	97.4	97.2
Petrillo et al.	99.5	99.5	77.1	75.4

n/a=not/applicable or information not provided.

a. **MIP only.**
b. **Protocol 1**
c. **Protocol 2**
d. **Protocol 3**
e. **Junior reader**
f. **Senior reader**
g. **Reader 1**
h. **Reader 2**

Different than the others, Chen et al. showed that the specificity of the method increased from 86.5% to 95% by adding DWI to AP (18). Moreover, using the diffusion sequence instead of the use of IV contrast has also been investigated due to the current published side effects, and complications of the use of IV contrast (38,39). Yamada et al. conducted the most way out study in the literature because they used no intravenous contrast material which is an indispensable part of breast MR. Their results showed that DWI based MIP images would be promising if supported by more comprehensive studies in the future (23). However, the addition of DWI sequences to the AP or using of IV contrast media is still highly controversial due to the absence of a standardized protocol.

4.Conclusion

AP breast MRI protocols or fast sequences, along with the shortening of the imaging time, can reduce the interpretation time of the images, and reduce the cost by maintaining a high diagnostic accuracy of full diagnostic protocol. However, reliability and application of abbreviated protocol and short sequences should be proven and standardized in larger and prospective series.

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CHAPTER V

LASER-ASSISTED SURGICAL METHODS FOR PATIENTS WITH BENIGN PROSTATE HYPERPLASIA: HoLEP vs ThuLEP REVIEW ARTICLE

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1. Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) are common in adult males (1). Transurethral resection of the prostate (TUR-P) is the gold standard surgical treatment in patients with prostate sizes less than 80 ml (2). Due to the limited applying of TUR-P in large prostate volumes and possible complications, alternative surgical methods have been improved. Holmium: YAG (Yttrium Aluminum Garnet) and Thulium: YAG are laser types for using in the surgical treatment of benign prostate hyperplasia (BPH) (3). Holmium Laser Enucleation of the Prostate (HoLEP) and Thulium Laser Enucleation of the Prostate (ThuLEP) are surgical methods independent of prostate size. HoLEP and ThuLEP have become an alternative to TUR-P in patients with a prostate volume less than 80 mL and alternative to open prostatectomy for prostate volumes greater than 80 mL (5).

In this study, comparing of Holmium and Thulium lasers in minimally invasive surgical treatment of BPH was investigated by literature.

2. Material And Method

A comprehensive search of PubMed/Medline and Embase database from 01 January 2008 to 31 December 2020. Inclusion criteria: full text publications in English language were included in the study. Exclusion criteria: case reports, letters, publications with editorial comments were excluded from the study.

3. Results

3.1. Holmium Laser

Holmium laser has a wavelength of 2140 nm. Holmium laser beams are strongly absorbed by water and fluids of cell (3). During the use of holmium laser, energy is released in short pulses. Holmium laser has 0.4

mm tissue penetration in prostate tissue (4). Holmium and thulium laser use normal saline to avoid hyponatraemia. Since the prostate tissue contains high water, it enables to perform coagulation and tissue ablation (3). The incision and dissection of the prostate tissue is performed by the tissue ablation and coagulation effect of Holmium laser (5).

In 1998, Gilling et al. described HoLEP operation (8). HoLEP can be applied regardless of prostate size. HoLEP is an alternative surgical method to TUR P and open prostatectomy in terms of efficacy, safety and complications (3).

3.2. Thulium Laser

The wavelength of the Thulium laser is 2013 nm. Energy is provided by continuous waves. Thulium laser has 0.25 mm tissue penetration in prostate tissue. (3). Because of short penetration depth, high energy density occurs. Effective vaporization and hemostasis provides image clarity during operation (6). Thulium laser can be used for laser vaporization, resection or enucleation.

In 2010, Hermann et al. described ThuLEP operation (12). Thulium laser is used effectively and safely in the surgical treatment of BPH like Holmium laser (5, 6).

3.3. Functional Results Of HoLEP And ThuLEP

Open prostatectomy is applied for LUTS caused by prostate sizes greater than 80-100 mL (7). HoLEP and ThuLEP are minimally invasive surgical methods that can be applied regardless of prostate size (8). Bach et al. followed up 90 BPH patients with a volume greater than 80 mL for 12 months after ThuLEP surgery. There was a significant improvement in International Prostate Symptom Score (IPSS), Quality of Life (QoL), maximum urine flow (Qmax) and post voiding residual volume (PVR) compared to the preoperative period. In the peroperative period, superficial ureteral orifice injury during enucleation was observed in 1 (1.11%) patient due to the enlarged median lobe. Stress urinary incontinence (SUI) was observed in 10 patients (11.11%) in the postoperative period. SUI improvement was observed in 8 of these patients within 1 to 6 months (9).

Morozov et al. performed a retrospective analysis of patients who had undergone one of three forms of endoscopic enucleation of prostate (EEP): HoLEP, ThuLEP or monopolar enucleation of the prostate (MEP). They compared intraoperative, early postoperative and 3rd-6th months follow-up complications. A total of 1413 patients were included in this study; 509 (36%) patients underwent HoLEP, 812 (57.5%) patients underwent ThuLEP and 92(6.5%) patients in MEP group. Clavien-Dindo grade 1 complication was ureteral orifice injury in 0.5% of the cases; 3 cases in HoLEP, 4 cases in ThuLEP, and none in MEP. The Clavien-Dindo

grade 2 complication in the early postoperative period was a fever of >38°C in 2.76% of patients; 2.95% cases after HoLEP, 2.46% cases after ThuLEP, 4.3% cases after MEP, p=0.56). In patients with prostate volumes <80 mL, fever was found in 3% of the patients after any type of enucleation. In patients with larger than 80 mL prostate volumes, fever was revealed 2.5% of the patients. Statistical differences were insignificant between the groups (p=0.3). Another common grade 2 complication was the necessity to delay morcellation due to intraoperative hemorrhage and consequent unsatisfactory visualization. This complication was found in 1.4% of cases; 2% in HoLEP, 1.2% in ThuLEP and 2.2% in MEP, p=0.27). This complication was found 1% cases of patients with prostate volume <80mL 1% in and 1.8% cases of patients with larger glands (p=0.09). It was observed that prostate volume did not produce any significant effect on complication frequency. The most frequently observed Clavien-Dindo grade 3 complication was bladder tamponade. The complication frequency of bladder tamponades was 2.2% after HoLEP, 2% after ThuLEP, and 4.3% after MEP (p=0.267). The tamponade frequency in the patients with prostate volumes <80mL and >80mL was 2% and 2.9%, respectively (p=0.4). Stress urinary incontinence was found in 3.9% of patients at 3 months and in only 1.4% of patients at 6 months after the operation. Urethral stricture at 6 months after the surgery was observed in 1.4% of patients. Bladder neck sclerosis was observed in only 0.9% of these cases. No significant difference was observed between these complication frequencies (10).

Gazel et al. in their randomized prospective study, HoLEP operation was performed on 119 patients with BPH whose prostate volume was greater or less than 80 mL. Enucleation time, morcellation time and total operation time were found to be significantly longer in the prostate volume greater than 80 ml group (p=0.001). It was observed that the tissue weight and total laser energy enucleated were significantly higher in the group with prostate volume greater than 80 ml (p=0.001). Enucleation efficiency and rate, morcellation and laser efficiency were observed similarly in the two groups. There was no statistically significant difference between the two groups in terms of Qmax, PVR, IPSS, and QoL score. In the group with greater than 80 ml volume, catheter removal time, hospitalization time and maximum voiding time were found to be significantly longer (p=0.005, p=0.01, p=0.002, respectively) (11).

Zhang et al. in a randomized controlled study, total of 116 consecutive patients with large prostate volume (>80 cc) were be treated surgically with either HoLEP (n= 58) or ThuLEP (n= 58). Follow-up was assessed at 1, 3, 6, 12 and 18 months after surgery. Enucleation and total operation time were significantly shorter in the ThuLEP group (p <0.001). There was no statistically significant difference between morcellation time,

removed tissue weight, decrease in hemoglobin, catheterization time and hospitalization time ($p > 0.05$). At the end of 18 months of follow-up, there was no significant difference between the two groups in terms of IPSS, PVR, QoL, and Qmax values. Postoperative hematuria was seen in 3 patients (5.2%) in the HoLEP group, 1 patient (1.7%) in the ThuLEP group; transient incontinence was seen 5 patients (8.6%) in the HoLEP group and 2 patients (3.4%) in the ThuLEP group; bladder mucosal injury was observed in 4 patients (6.9%) in the HoLEP group and 1 patient (1.7%) in the ThuLEP group ($p > 0.05$). No significant difference was observed between the two groups in terms of bladder neck contracture and urethral stricture at 12 and 18 months of follow-up (12).

Studies show that HoLEP and ThuLEP are an effective treatment method in patients with prostate volumes greater than 80 mL. HoLEP and ThuLEP are minimally invasive prostate surgeries that can be an alternative to open prostatectomy.

3.4. Effects Of HoLEP And ThuLEP On Continence

After HoLEP surgery, the prevalence of SUI is between 4.9-12.5% (13). SUI complaint resolves within 6 to 12 months in most patients (14). Saitta et al. reported the SUI rates after HoLEP surgery at the 1, 3 and 6 months follow-up as 5.8%, 1.5% and 0.7%, respectively (15). Minagawa et al. reported the incidence of SUI as 3% at the 3 month after HoLEP (16). Krambeck et al. reported the incidence of incontinence as less than 5% in their 1000 cases of HoLEP series (17). Alkan et al. in their retrospective study, postoperative SUI after HoLEP was reported as 1% (18).

Elmansy et al. in their retrospective study, they included 949 patients by scanning 10-year data. They found that prostate volume greater than 81 gm, operation time more than 96 minutes, PSA value decrease of more than 84% and the presence of diabetes mellitus were significantly associated with the development of SUI in patients undergoing HoLEP ($p < 0.02$, $p < 0.01$ and $p < 0.001$, respectively) (19). In a multi-center, prospective and randomized study, functional and complication results of HoLEP and TUR-P compared. Transient urge incontinence was similar between the two groups; dysuria was found to be more common in the HoLEP group ($p = 0.0002$) (20). In the early postoperative period, SUI was observed at similar rates in patients who underwent HoLEP, TUR-P, and open prostatectomy (2%) (6, 20, 21).

Transient urinary incontinence after ThuLEP was reported as 0.5-6.7% (3). Iacono et al. reported temporary urge incontinence rate as 6.7% after ThuLEP in 148 patients (22). Yuan et al. reported the late period SUI rate as 0.5% in 188 patients who underwent ThuLEP (23). Sun et al. in a multicenter prospective study involving 2216 patients, SIU was reported as 0.1% after thulium laser prostate resection (24). Xia et al. compared

ThuLEP and TUR-P in a randomized prospective study and there was no significant difference between the two groups in terms of stress incontinence (p = 0.48) (32).

Studies showed that after HoLEP and ThuLEP surgery incontinence rates decrease in follow-up.

3.5. Effects Of HoLEP And ThuLEP On Sexual Functions

The association of erectile dysfunction (ED) and BPH is common in patients with LUTS (25). Kim et al. in a prospective study involving 60 patients who were sexually active with a median age of 68.5 years. They investigated the sexual functions of patients who underwent HoLEP for BPH by using the Male Sexual Health Questionnaire (MSHQ). There was no significant difference in erection, ejaculation, anxiety and sexual desire at the 6th month after the operation (p> 0.05). Decrease of sexual satisfaction score due to retrograde ejaculation was observed in 38 patients (63.3%) (26). Pushkar et al. in their prospective study compared HoLEP and TUR-P in terms of postoperative erectile functions by using the International Index of Erectile Function (IIEF-15) score. The groups are divided into two groups as younger than 55 years old and older age group. In HoLEP group patients IIEF-15 score was normalized at the 6th postoperative month, but remained significantly lower in older age groups. In TUR-P group, the IIEF-15 score was found to be significantly lower in all age groups. Patients greater than age of 55 who underwent HoLEP or TUR-P, the IIEF-15 score changing at 3rd and 6th months were not statistically significant (p> 0.05) (27). Alkan et al. reported that there was no change in postoperative IIEF-5 scores in long-term follow-up after HoLEP (18). Capogrosso et al. in their study mean follow-up period was 152.1 months and they included 135 patients. They observed decrease in the average IIEF multidimensional score in the long-term patients who were applied HoLEP (28).

In a prospective study, investigated the effects of ThuLEP on erectile and ejaculatory functions. There was no significant difference in IIEF-5 scores at postoperatively 4th and 8th months compared to preoperative values (p=0.195 and p=0.26, respectively). Ejaculatory function assessed by Male Sexual Health Questionnaire-Ejaculatory Disease (MSHQ-EjD) and a significant reduction in ejaculation was observed (p <0.0001) (29). Enikeev et al. compared ThuLEP and TUR-P in terms of erectile function. Included 469 patients data were analyzed and it was shown that there was no significant difference between preoperative and postoperative IIEF-5 scores in the ThuLEP group (p= 0.08). Mean IIEF-5 score was shown significant increase in the ThuLEP group (0.72) and comparing to decrease in TUR-P patients (0.24) (p <0.001) (30). Carmignani et al. in a prospective study involving 110 patients with mean

age of 67.83 years. There was no significant difference in the preoperative and postoperative erectile functions of the patients at the 3rd and 6th months after ThuLEP. Postoperative ejaculatory functions were evaluated with MSHQ-EjD, and preservation of ejaculatory function was demonstrated in 58 patients (52.7%) after ThuLEP. Painful ejaculation was observed in 7 (12.1%) of 58 patients (31). Xia et al. They found that retrograde ejaculation was seen in 55% after ThuLEP and 65% after TUR-P (p=0.42) (32).

3.6. HoLEP And ThuLEP On Anticoagulant-Antiplatelet Drug Use

Anticoagulant (AC) or antiplatelet (AP) use is common in patients with BPH. With the use of laser in BPH surgery, the amount of bleeding and blood transfusion rate were expected to decrease. Agarwal et al. performed a retrospective review of HoLEP patients on AP and AC therapy compared to none. There were no differences in morcellation time, enucleation time, total operation time and amount of laser energy. There were no difference in postoperative trial passage and hemoglobin drop. Postoperatively, there was a higher complication rate in AP and AC groups in 90 days (p=0.035), but there was not an increase in Emergency Department visits (p=0.557) or Clavien 3 complications (p=0.16). (33). Yuk et al. investigated the efficacy and complication rate in HoLEP surgery due to discontinuation of antithrombotics. There were 248 (25.96%) patients in antithrombotic drugs use group and 707 (74.04%) patients in non-antithrombotic group. Seventy-five (66.5%) and 70 patients (28.2%) discontinued the antithrombotic therapy 5–7 days and <1 week preoperatively, respectively. Three patients (1.21%) were switched to low-molecular-weight heparin therapy, and 10 (4.03%) continued antithrombotic therapy. There were no significant differences in the incidence rates of postoperative transfusion (p=0.894), thrombosis (p=0.946), haemorrhage requiring bladder irrigation (p=0.959), complications from antithrombotic use, transurethral coagulation (p=0.894), cardiovascular events (p=0.845) and cerebrovascular events (p=0.848). Efficacy and complications related to the short-term antithrombotic withdrawal before and no significant differences also showed after HoLEP (34). Tayeb et al. compared 116 patients who required AC / AP treatment and 1558 patients who did not required. Significant differences were observed in enucleation times (51 min vs 65 min, respectively, p <0.001) and morcellation rate (5 g / min vs 4.5 g / min, respectively, p = 0.02) in patients AC / AP using and not using. Hospitalization time (27.8 hours vs 24 hours, p <0.001) and the continuous bladder irrigation time (15 hours vs 13.5 hours, p <0.001) were observed significantly longer in patients using medication. There was no significant difference in postoperative transfusion rate (3.5% and 1.6%, p = 0.128).

They reported that the use of intermittent or continuous anticoagulant therapy did not adversely affect outcomes of HoLEP (35).

Becker et al. compared the results of patients who used oral anticoagulants (n=94) or vitamin K antagonists (n=151) and those who did not use any anticoagulants. They observed the mean hemoglobin decrease significantly more in anticoagulants or vitamin K antagonists using group. The mean catheterization time and hospitalization time were significantly longer in drug users than in non-users ($p < 0.001$). Blood transfusion was performed in 1 patient (1.3%) in the oral anticoagulant group, 3 patients (2.2%) in the vitamin K antagonist group and 4 patients (0.2%) in the control group. Statistical differences were found to be significant compared to the control group ($p < 0.001$) (36). In a meta-analysis published by Zheng et al, a lower rate of blood transfusion and bladder tamponade was found in who did not use antithrombotics ($p<0.0001$ and $p=0.004$, respectively). Shorter operation time was observed in the not using group ($p<0.00001$). Hemoglobin decrease and hospitalization time were similar between the two groups ($p= 0.63$ and $p= 0.90$, respectively) (37).

More studies are needed on the efficacy and safety of ThuLEP in patients using AC / AP.

3.7. HoLEP And ThuLEP On Elderly Patients

BPH patients may be at high risk in the presence of significant comorbidities and with increasing age. Piao et al. investigated the effectiveness of HoLEP in patients with different age groups. It was found that age group over 80 years old (n = 38) had significantly longer enucleation time, morcellation time, and total operation time compared to the lower age groups ($p = 0.002$, $p = 0.010$ and $p < 0.01$, respectively). In patients over 80 years old, significant decrease was observed in the maximum micturition rate on the uroflowmeter at postoperative 2nd week and 3rd month ($p < 0.01$ and $p = 0.004$, respectively). A significant difference was observed in terms of IPSS between the groups at postoperative 6th month ($p < 0.05$) (38). In a study involving 412 patients comparing the ThuLEP results in over and below 75 years of age. There was no significant difference between the two groups in terms of IPSS, Qmax, QoL, reoperation rate, median operation time, catheterization time and hospitaization time at 1-year follow-up (39).

Morozov et al. performed a retrospective analysis of patients who had undergone HoLEP, ThuLEP or MEP. They compared complication rates in two groups: 626 (44.3%) patients aged 65 years or younger and 787 (55.7%) patients older than 65. Stress urinary incontinence after 3

months was found 3.4% of patients aged 65 years or youngers and 4.3% of patients older than 65 (p=0.2). Urethral stricture was found 1.4% both of the groups (p=0.5). Bladder neck sclerosis was found 1.1% of patients aged 65 years or youngers and 0.8% of patients older than 65 (p=0.2) (10).

4. Conclusion

When HoLEP and ThuLEP are compared with other minimally invasive BPH surgeries and open prostatectomy, their functional outcomes and complications are comparable. HoLEP or ThuLEP operation can be applied safely in patients with large prostate volume by minimally invasive surgery and can be applied safely in patients using anticoagulants.

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CHAPTER VI

CATAMENIAL PNEUMOTHORAX

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1. An Overview of Pneumothorax

Pneumothorax is defined as the accumulation of air in the intrapleural space and the resulting lung collapse [1]. (Figure)

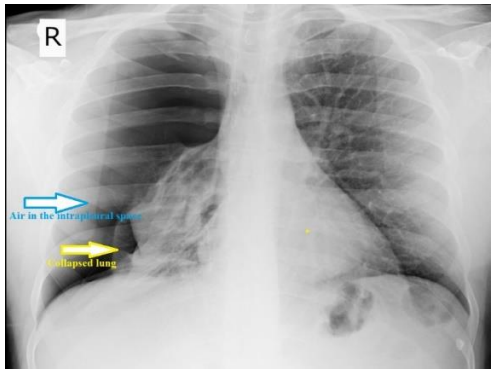

Figure: Demonstration of pneumothorax on Chest X-ray

The term of pneumothorax was first used by Itard in 1803 [2]. It is more common in male sex [1]. Its incidence is 18-28 / 100000 in male gender and 1.2-6 / 100000 in female gender [2]. It is frequently observed in smokers, those with bullous lung parenchyma, those with weak and tall body types and ıts frequency is highest in the 30s ages [1,3].

Usually, sudden onset chest pain and dyspnea are the most observed symptoms. Severity of the symptoms can be mild or very high [4]. Especially in cases such as tension pneumothorax, very severe symptoms and signs can be observed. On physical examination, a decrease in respiratory sounds and hyperresonance can be detected in the hemithorax, where is pathology. Radiological imaging methods play a key role in the diagnosis of pneumothorax. Radiological imaging methods are helpful in both

evaluating the extent of the pathology and making decisions for treatment choices [2]. Chest radiographs, ultrasound (USG), and tomography (CT) can be used to detect air collected in the intrapleural space and to monitor the follow-up-treatment course. The method of treatment varies depending on the presence of symptoms, the history diseases of the patient and the rate of pneumothorax. As treatment methods; With continuous oxygen therapy, observation, needle aspiration or percutaneous drainage, tube thoracostomy and operation can be performed in necessary patients.

In 1932, Kjaergaard defined pneumothorax in healthy individuals as primary spontaneous pneumothorax except disease or traumatic occurrence [2,5]. Pneumothorax can be grouped mainly as spontaneous and non-spontaneous. (Table)

Table: Pneumothorax Classification

SPONTANEOUS	NON-SPONTANEOUS
1-Primary Spontaneous Pneumothorax	1-Traumatic
2-Secondary Spontaneous Pneumothorax	2-Iatrogenic
3-Catamenial	
4-Neonatal	

2. Catamenial Pneumothorax

Catamenial pneumothorax (CP) is the recurrent accumulation of air in the intrapleural space and lung collapse in women who do not have any other lung disease. Pneumothorax may not be seen in every menstrual period [1].

The origin of the word catamenial is Greek and means 'monthly' [2]. CP was first described in 1972 by Lillington et al. [6]. In daily practice there is little awareness of CP and is often thought of as a simple case of pneumothorax [6]. It is more common in the 30s-40s ages [7]. Catamenial pneumothorax constitutes 2.8-5.6% of spontaneous pneumothoraces [7,8] and its actual rate is estimated to be higher [6]. It is seen that the Turkish and English literature generally consists of case reports alone or small number of series which consists of limited number of cases. In fact, until 2019, the number of pneumothorax cases associated with the menstrual cycle in the literature is 350 [6].

CP is often accompanied by pelvic endometriosis (%55) [2,9]. Anyway, one of the areas where endometriosis is most frequently observed outside the pelvic area is the thorax [2]. Implants can be observed in the visceral-parietal pleura, lung parenchyma, bronchial system and diaphragm. Implants are more common in the diaphragm [6,9]. CP is often

associated with thoracic endometriosis in the pleura and lung parenchyma [10]. Although different anatomical and hormonal theories such as lymphagenic or hematogenic spread, and transdiaphragmatic transmission have been proposed in its etiology, the etiology has not been fully elucidated [6,9]. There are some reasons for the build-up of air in the intrapleural distance. Firstly, air leakage may take place from the genital organs into the thorax through the diaphragm openings (fenestration) created by endometriosis, secondly, air leakage from the lung may be linked to the alveolar damage caused by increased prostaglandin F2 level in the blood during menstruation, thirdly, the build-up of air may stem from focal endometrial implants [11]. It is also one of the reasons suggested when local hyperinflation caused by implants in the terminal bronchioles causes pneumothorax by creating a check-valve mechanism [6]. Satisfactory explanations have not yet emerged for matters such as why the use of anti-inflammatory drugs that reduce the prostaglandin level cannot prevent pneumothorax, why more frequent pathology is observed in the right hemithorax[8], and how endometrial tissue reaches the thoracic area [2].

CP typically occurs 2-3 days before the menstruation [2,11]. Recurrences coinciding with the menstrual cycle are observed and are frequently (85-95%) observed in the right hemitoarks [6,7,11]. Chest pain, dyspnea, cough, hemoptysis may be observed, hemothorax may occur in the affected hemithorax [2,6]. The most common symptoms are pain and dyspnea [8]. The severity of the symptoms can vary from person to person and even during each pneumothorax period. It can sometimes be asymptomatic. Generally, findings observed in pneumothorax are detected in physical examination.

When evaluating the patient in terms of CP, the history of the disease (especially endometriosis), the frequency of pneumothorax and its relation with the menstrual cycle should be questioned. Although the pre-diagnosis is often made by clinical evaluations and anamnesis, the definitive diagnosis is made after anatomical or histopathological findings. Radiological imaging methods have an important role in diagnosis. While pneumothorax, lung nodule, pleural fluid (hemothorax), which are mostly indirect findings, can be observed with chest radiographs, tissues belonging to the endometrium can be detected in CT and especially MRI [8]. Active glandular tissues can be detected in T2-weighted images of MRI applied during menstruation [12]. Although there is not a laboratory parameter for definitive diagnostic, it has been reported that it may be associated with serum Ca125 antigen level, but this parameter is not suitable for routine use [6,7].

There is no definitively accepted diagnosis-treatment algorithm for CP. Although important information can be obtained in terms of diagnosis

with anamnesis, physical examination and radiological imaging methods, surgical procedures may be required for definitive diagnosis. Care should be taken in the diagnosis abouth CP in young female sexed patients with a history of right-sided recurrent pneumothorax and endometriosis.

The main treatment strategies are surgical and medical-hormone therapies. Surgical treatment is more effective than hormone therapy [13]. After surgical treatment recurrence rates are in the range of 14.3-55% [7,9]. It has been reported that a high success rate has been achieved in cases where surgical treatment and medical treatment are applied together [2,6,13]. Video-assisted thoracic surgery (VATS), one of the surgical methods, is a recommended method for both diagnosis and treatment [8]. Its application especially during menstruation will increase the chance of detecting diaphragmatic lesions [1]. Surgical treatments are closure of diaphragm fenestrations, diaphragm plication or reconstruction, electrocoagulation or excision of endometriosis areas, chemical pleurodesis, wedge resection from the lung parenchyma, hysterectomy or bilateral oophorectomy. Medical treatment options are oral contraceptives, danazol, progesterone derivatives and GNRH analogues [2,8,11]. It is essential that thoracic surgeons, gynecologists and endocrinologists work together in the treatment of CP.

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CHAPTER VII

THE USE OF HOMOLOGOUS PLATELET-RICH PLASMA FOR THE TREATMENT OF KNEE OSTEOARTHRITIS

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1.Introduction

Osteoarthritis is the common form of arthritis and a major cause of morbidity, activity limitation, physical disabilities, excess healthcare utilization, reduced health-related quality of life, and excess mortality, especially in people aged 45 years and above (1).The goals of osteoarthritis treatment include the alleviation of pain and improvement of functional status (2). Today, the majority of treatment modalities are palliative, including oral or topical nonsteroidal anti-inflammatory drugs. However, lifestyle modifications, particularly exercise and weight loss, are also effective (3,4). Recent research has focused on new methods for replacing or stimulating the repair of the damaged cartilage. Platelet-rich plasma (PRP) is a key source of the growth factors that are involved in tissue repair and regeneration.

Growth factors include platelet-derived growth factor (PDGF-AA, -BB, and -AB isomers), transforming growth factor (TGF-β1 and -β2 isomers), platelet factor 4 (PF4), interleukin-1 (IL-1), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen (Fg), vitronectin (Vn), fibronectin (Fn), and thrombospondin-1 (TSP-1) (5).

These products deliver collections of bioactive molecules with important roles in fundamental processes, including inflammation, angiogenesis, cell migration, and metabolism, in pathological conditions. PRP is not only crucial in the repair of damaged structures but also in creating biological models that encourage tissue regeneration by improving the metabolic functions of those structures (6).

Recent papers have investigated the effects of PRP on cartilage repair. For instance, Kütük et al examined the action of PRP on cartilage repair in temporomandibularjoint osteoarthritis in rabbits (7). Using scanning electron microscopy, the researchers found thick and disorganized collagen fibrils in the control group and thin, well-organized collagen fibers in the PRP group. Histologically, the regeneration of the fibrocartilage and hyaline cartilage was higher in the PRP group.

Although the molecular in vivo effects of PRP must be investigated further, clinically, autologous intra-articular injection for the treatment of knee osteoarthritis is widely accepted and increasingly used to treat patients.

Autologous PRP is derived from a patient's own peripheral blood, which is then centrifuged to achieve a high concentration of platelets within a small volume of plasma. It is then reinjected at the injury site or inserted as a gel or other biomaterial during surgery. Various blood separation devices require differing preparation steps, essentially accomplishing similar goals. About 30–60 ml of venous blood is drawn by an aseptic technique from the antecubital vein. The use of an 18- or 19-g butterfly needle is advised to avoid irritation and trauma to the platelets, which are in a resting state. The blood is then placed in an FDA-approved device and centrifuged for 15 min at 3,200 rpm. Afterward, the blood is separated into platelet-poor plasma (PPP), red blood cells (RBCs), and PRP. Next, the PPP is extracted through a special port and discarded. While the PRP is in a vacuumed space, the device is shaken for 30 s to resuspend the platelets. The PRP is then withdrawn. Depending on the initial blood draw, there will be approximately 3–6 cc of PRP available (8).

PRP can also be prepared as random donor platelet concentrates from whole-blood-derived platelets or as apheresis platelets from a single donor (9).

In the whole blood (WB) harvesting method, 500 ml of blood is collected and stored in a citrate preservative at room temperature. Within 8 h, the blood is centrifuged at a slow spin, and the PRP is separated into an attached empty satellite bag. The PRP is centrifuged again at a fast spin and separated into 1 unit of platelet concentrate. Each unit of platelets contains 5.5 × 1010 platelets in 50–70 mL of plasma. Alternatively, platelets can be isolated from WB from the buffy coat layer by centrifugation of the WB in bags designed to remove RBCs and plasma through a tubing at the bottom and top of the bag. The platelet-enriched buffy coat is further processed (through centrifugation and/or leukoreduction filters) to eliminate white blood cells (WBCs) and any remaining RBCs. This method is employed in Europe and Canada. It

permits the storage of WB at room temperature for up to 24 h prior to platelet harvesting and provides some other advantages.

Apheresis platelets or single-donor platelets are obtained by performing apheresis on volunteer donors. During this procedure, large volumes of WB are processed in an extracorporeal circuit and centrifuged to separate the components. The RBCs and a certain percentage of the plasma are returned to the donor. A single donor on apheresis donates an equivalent of >3.0 × 1011 (6 units) of WB-derived platelets suspended in a volume of 200–400 mL of plasma. Single-donor apheresis-derived platelets minimize the number of donor exposures to which the transfusion recipient is exposed and have become the primary source of platelets in the United States (10).

The PRPs derived from other donations are routinely used for intravenous transfusion to patients with neoplastic or gastrointestinal diseases or diseases of the blood-forming organs in an effort to prevent or treat bleeding due to thrombocytopenia (11). It is also known that the administration of ABO-specific platelets is not strictly required because platelet concentrates contain few RBCs. In additional, platelets derived from Rh-positive donors are often transfused to Rh-negative patients.

Therefore, the uncomplicated attainability of homologous platelet suspensions in addition to the high concentration of platelets within small (50–70 cc) suspensions and the very low antigenic potential suggest that intra-articular injection of homologous PRP (H-PRP) might be effective in the treatment of degenerative osteoarthritis. Thus, in this preliminary study, the effects of H-PRP in the treatment of degenerative knee osteoarthritis were evaluated by performing intra-articular H-PRP injections in 52 patients with 6-month follow-ups.

2. Material and Methods

This study was approved by our institutional ethics committee (Clinical Research Ethics Committee of Necmettin Erbakan University, Meram School of Medicine). The diagnosis of osteoarthritis was based on the American College of Rheumatology (ACR) criteria (12) and the Ahlbach's radiological classification system based on AP weight bearing and lateral views of knees was used for staging of the disease.

The patients have chronic pain (at least 3 months) with no benefit from previous analgesic treatments or physiotherapy and the presence of grade 3–4 osteoarthritis according to the Ahlbach's classification system were included in current study.

Exclusion criteria were visco supplement or corticosteroid injections into the affected knee, previous knee surgery, previous knee trauma, presence of knee joint infection, systemic disorders such as diabetes and

rheumatoid arthritis, and patients undergoing therapy with anticoagulants or antiaggregants.

There were 25 men and 27 women, and their mean age was 58.77 (range: 47–70) years. The average body mass index was 34.74. All the patients were informed about the results of the process before the application of H-PRP injection. The injection was performed on those patients who were willing to undergo the procedure and signed the consent forms. The injection was performed bilaterally in 9 patients and unilaterally in 43 patients; a total of 61 knees were injected (Table 1).

2.1. Homologous PRP preparation

WB donations (450 mL) from subjects with the same blood groups as those of the patients were collected into quadruple blood bag systems after ABO- and RhD-compliance was confirmed for all patients. The H-PRP was collected by the buffy coat method. The WB was centrifuged at high speed with subsequent collection of the buffy coat. The buffy coat was then centrifuged at low speed to concentrate the platelets and remove RBCs and WBCs. The WB was then centrifuged at 3000 × g for 23 min. The supernatant plasma from the top of the container and the RBCs from the bottom of the container were removed using an automated instrument. Next, the obtained buffy coat was recentrifuged for 5 min at 400 × g (low speed), and approximately 50 mL of PRP was transferred into a platelet storage bag by an automated instrument.

2.2. Injection technique

All injections were carried out in an outpatient setting.The homologous material was evaluated the presence of any infectious diseases prior to administration in all cases. The injection was performed at the affected knee with a classical approach to the upper pole of the patella using a 22-g needle. No ultrasound guidance was employed. After cleaning the skin with an antiseptic solution, 5 ml of H-PRP was injected into each affected knee. After injection, passive flexion and extension was performed several times, and the patient rested in the supine position for 5–10 min. Patients were allowed to use paracetamol as required (maximum 2 g/day) if they felt pain, but they were asked not to use any analgesic within 24 h before evaluation and avoid intense physical activity.

2.3. Follow-up

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores were used to investigate the clinical effects of the treatment. The WOMAC is a proprietary set of standardized questionnaires widely used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. The WOMAC have five items for pain,

two items for stiffness, and 17 items for functional limitation. Physical functioning questions cover daily activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties (13). The scores were evaluated before and after the injection at months 1 and 6. Complications and adverse effects were also evaluated.

2.4. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows® software program version 18.0. Intergroup comparisons were made using the analysis of variance for repeated measures. To determine the statistically different groups, the Bonferroni-corrected paired t-test was used. A Pvalue of <0.05 was statistically significant.

3. Results

No severe adverse events or complications related to the injections were observed during the treatment or follow-up period. All patients were satisfied with the H-PRP treatment, especially regarding pain relapse, and no patients underwent knee surgery due to pain or functional limitations of the knees. A statistically significant improvement in all WOMAC scores was observed at months 1 and 6 compared to the preinjection values ($P = 0.00$). The positive effect on pain continued up to 6 months. However, at month 1, it was significantly better than that at month 6 ($P \leq 0.05$). Between months 1 and 6, the knee joint stiffness showed no statistically significant difference ($P \geq 0.05$), as it was stable at the 6-month follow up. However, both of them were better than the preinjection values. Similar to the pain scores, the physical function showed further improvement at the 6-month follow-up ($P \leq 0.05$). There was no statistically significant difference between months 1 and 6 in social functioning ($P \geq 0.05$). Emotional functioning was also improved during the follow-up periods ($P \leq 0.05$) (Table 2, 3).

4. Discussion

Intra-articular injections of autologous PRP have been widely accepted for the treatment of knee osteoarthritis. In addition to the treatment of chronic osteoarthritis, autologous PRP is also commonly used in sports medicine to treat injuries of the tendons, ligaments, and muscles (14,15,16).

Recently, the efficacy of autologous PRP for treating degenerative osteoarthritis has also been investigated in several studies (17,18,19). Clinical improvement, especially in terms of pain after knee movement and at rest, was reported.

In this study, we applied H-PRP derived from WB donations to treat chronic degenerative osteoarthritis using a method different from the standard autologous PRP. No complications or adverse effects due to H-PRP injections were observed. After the treatment, all the patients reported a significant reduction of pain at rest and movement. Moreover, all the patients reported a significant increase in the quality of their lives at the 6-month follow-up with only one H-PRP injection.

Crovetti et al reported about topical H-PRP application to treat chronic ulcers, including diabetic, venous, and neuropathic ulcers. They observed no adverse effects but faster promotion of granulation tissue and decreased pain in all cases (20).

However, the use of intra-articular injections of H-PRP has not been reported previously. The present study showed that intra-articular injections of H-PRP could be used safely and also exert positive effects similar to those of autologous PRP in the treatment of degenerative osteoarthritis.

All the donated blood samples are carefully tested for transfusion-transmissible infections (TTIs), including HIV, hepatitis B, hepatitis C, and syphilis. The H-PRP, like other blood transfusions, has achieved a high degree of safety regarding the transmission of viral diseases. The homologous material was tested for the presence of any infectious diseases prior to administration in all our cases.

Based on our study results, the advantages of homologous PRP versus the autologous PRP are as follows:

H-PRP can be easily obtained from blood centers and prepared from the blood of healthy donors without contact with the outside environment; therefore, the risk of infection is minimal.

Due to the interaction with autologous PRP in the preparation phase of the external environment, we believe that there might bea higher risk of contamination.

H-PRP application is completed with a single injection. However, two injections are performed in autologous PRP treatment. The patient's own blood is collected for the first injection to prepare autologous PRP. It is then injected into the joint. Therefore, autologous PRP application is more painful and uncomfortable than H-PRP application for the patient.

Autologous PRP application requires 30–35 min. First, the blood is collected from the patient, followed by in vivo autologous PRP preparation and then intra-articular injection. However, a single intra-articular injection of H-PRP into the joint requires a maximum of 5 min. Therefore, it is faster and more practical than autologous PRP.

To obtain 5 ml of PRP, approximately 50 ml of blood must be collected from each patient, and a minimum of 80–100 ml of blood is required for both knees. This process can intensify anemia in anemic patients, but H-PRP does not carry such a risk.

In addition, there is a possibility that growth factors released from the platelets of H-PRP might have stronger regenerating effects because they are obtained from healthy donors. In this regard, the superiority of H-PRP must be tested in more comprehensive, long-term studies.

Despite the high number of patients evaluated, the absence of a control group and the lack of testing of H-PRP samples to confirm the contents and standardization are limiting factors in this study. Although the WOMAC score is a highly valuable instrument, the score can depend on the patients' condition on the day they completed the questionnaire. In future studies, the evaluation should be performed using a more objective measurement as well as radiological images. In addition, despite the low risk, obtaining written consents from the patients could be difficult in some scenarios; our patients were fearful and anxious about potential prosthesis surgery of the knee joint, and therefore, they accepted the H-PRP treatment as a new treatment modality.

In conclusion, this preliminary study showed that intra-articular injections of H-PRP could be safely used without complications or adverse effects. It also has positive effects on the degree of pain and the level of physical and social activities in the treatment of chronic knee osteoarthritis like autologous PRP. Therefore, it could be used as an alternative method to autologous PRP in suitable cases.

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CHAPTER VIII

IRON DEFICIENCY ANEMIA IN PREGNANCY

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1. Description

Anemia is defined as low hemoglobin (Hb) concentration of blood. Iron deficiency continues to be a major problem for pregnant women around the world. It always has a place in current issues. Increasing red blood cell and hemoglobin production in the first trimester of pregnancy causes a physiological expansion in plasma volume (1).

It is necessary to distinguish between iron deficiency anemia and physiological anemia due to the negative effects that may occur on the mother and fetuses during pregnancy.

2. Causes of anemia in pregnancy

During pregnancy, iron consumption increases as the weeks progress during pregnancy due to the increase in blood volume and increased fetal requirements. Physiological anemia and iron deficiency anemia are the two most common causes of anemia in pregnant women. The blood volume increases by 30-50% due to the increase in plasma volume during pregnancy. The increase in erythrocyte volume is more than the increase in plasma volume. As a result of this situation, physiological anemia occurs. This situation is at their maximum levels during the 20-24 gestation week (2). Iron requirement is lowest in the first trimester.It is gradually increases and reaches the maximum level in the third trimester due to fetal growth and increasing fetal needs. A total of 1000mg of iron is required during pregnancy. If this value will be detailed, 1gr (1000mg) iron; 300mg for fetus, 50mg for placenta, 450mg for increased erythrocyte mass, 240mg for maternal essential basal iron use (3)(4). The general causes of anemia are summarized in table 1.

Table 1 Causes of Anemia

Insufficient intake with diet	Fe, Folic acid Vitamins A, C and B12
Erythrocyte diseases and hemoglobin disorders	Thalassemia Sickle cell anemia Malaria Glucose 6 Phosphate Dehydrogenase Enzyme Deficiency
Chronic diseases	Tuberculosis (TBC) Chronic kidney disease (CRF) Cancers Rheumatic diseases Sexually transmitted diseases (Syphilis, gonorrhea, HIV etc.)
Conditions that disrupt iron absorption, bleeding, infection	Parasitic diseases (Helminthiasis, Amebiasis, Giardiasis, Schistosomiasis) Iron metabolism disorder Bleeding hemorrhoids Antepartum bleeding Multiparity Gastric bypass Inflammatory bowel diseases

3. Causes of iron deficiency anemia during pregnancy

Iron deficiency anemia is the second most common anemia after physiological anemia during pregnancy. It is very common not only in pregnant women but also in women of reproductive age. Many factors can contribute to iron deficiency. One of the most common causes is insufficient iron intake with diet. Most women have iron deficiency anemia due to nutritional deficiency in developing countries. In women of reproductive age, additional iron support to daily iron intake is required during menstruation and this value is on average 0.8 mg/day (4).

Generally, during pregnancy respectively, for increased maternal blood volume, fetal blood cells and fetal growth, a total of 500mg, 300mg, 350mg iron is required. The need for iron gradually increases as the trimester of pregnancy progresses (figure 1) (4). Approximately 250 mg of iron is lost during labor.

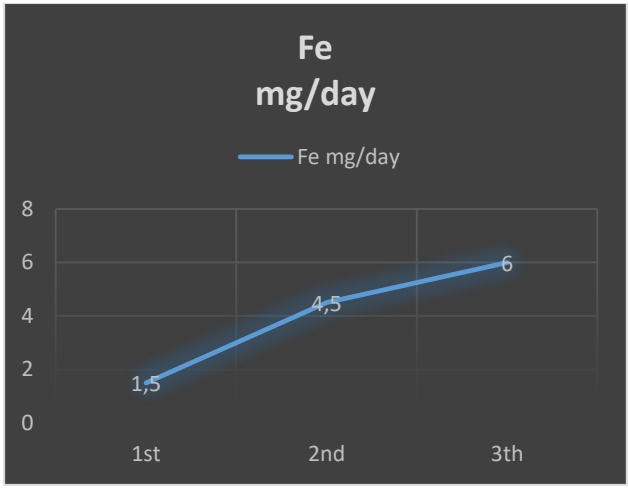

Figure 1. As the trimester of pregnancy progresses, the daily iron requirement increases. 1st trimester 1-2 mg/day, 2nd trimester 4-5mg/day, 3rd trimester 6mg/day.

In addition to all these needs, that affect iron absorption such as inflammatory bowel disease, bariatric surgery and not taking adequate iron supplements during pregnancy can cause anemia.

a) Increased iron requirement:

Iron consumption increases due to increased blood volume and increased fetus requirements during pregnancy.Although iron absorption increases during pregnancy, dietary iron intake is not sufficient to meet the need; therefore iron supplementation is required.

b) Insufficient iron stores:

- Insufficient intake with nutrition
- Multiparity (number of multiple births) -abortus
- Infections and especially parasitic diseases cause iron stores to empty or remain at low levels.
- Digestion / absorption disorder.

4. Signs and symptoms of iron deficiency anemia

Although some of the patients are asymptomatic, some patients may be accompanied by signs and symptoms on the table (Table 2). Although patients do not have anemia, symptoms may be observed due to low iron levels and ferritin.

Table 2 Iron deficiency symptoms and signs

Symptoms	Signs
●Fatique	●Pallor
●Weakness	●Dry or rough skin
●Headache	●Blue sclera
●Irritability	●Atrophic glossitis with loss of tongue papillae accompanied by tongue pain or dry mouth
●Exercise intolerance	●Cheilosis (also known as angular cheilitis)
●Exercise dyspnea	●Koilonychia (spoon nails)
●Vertigo	●Chlorosis (pale, pale green skin; extremely rare)
●Angina pectoris	●Alopecia (rare) especially in severe cases

Table 3 Effects of anemia on mother and baby in pregnant women

Maternal	Fetal
Postpartum infection	Low birth weight
Infection during pregnancy	Preterm labor
Antepartum bleeding	Impaired motor development and coordination
Placental abruption	Growth and development restriction
Postpartum bleeding	Very low birth weight
Preeclampsia	Congenital anomaly
Premature rupture of membranes	Susceptibility to infections/lack of resistance
Need for transfusion	Lack of attention
Placental malaria	Neonatal death
Postpartum depression	Neurodevelopmental delay
Cessation of lactation	

5. Support dose, duration of treatment and time to start treatment

Different suggestions come up after the studies in literature. For example; providing iron support to all women and menstruating adolescents, iron supplementation during pregnancy and the postpartum period, and late clamping of the umbilical cord during delivery are on the agenda (5). In another study, it is recommended to use mebendazole and

albendazole for the treatment of parasites that reduce iron absorption during pregnancy (6).

Iron supplementation is recommended for 6 months from the second trimester and for 3 months after birth, taking into account the daily iron requirement of all pregnant women, within the iron support program published by the World Health Organization and the Ministry of Health in our country (40-60mg/day for 9 months)(7).

6. Treatment of anemia in pregnant women

Iron deficiency treatment in pregnant women is important in terms of providing adequate support during and after delivery. Oral iron preparations preferred in pregnant women with insufficient iron stores have gastrointestinal side effects. Oral iron preparations used daily accumulate in high concentrations in gastrointestinal mucosa cells and lumen and iron absorption gradually decreases. Intestinal mucosa cells renew themselves in 5-6 days. Therefore, it has been reported that weekly iron therapy instead of daily iron therapy improves gastrointestinal absorption and patient compliance (8).

A significant reductions maternal anemia and low birth weight risk (3%) was found with prenatal iron supplementation. For every 10 mg increase in daily iron intake rate;15 grams increase occurs in the baby's birth weight. 1 g/dl increase in hemoglobin concentration in the third trimester or birth causes an increase of 143 g in birth weight (4). In studies, there was no decrease in preterm delivery risk of pregnant women who received iron support.

a) Oral iron therapy

Most women with iron deficiency, especially those diagnosed in the first trimester, prefer oral iron treatment. Oral iron is safe, cheap and readily available. For many women, this is adequate therapy. Iron sulphate is the most commonly prescribed oral formulation.

Recommended oral iron doses range from 40 to 200 mg of elemental iron per day. Generally, 60mg of elemental iron is preferred. Absorption can be improved by taking vitamin C along with iron and also by avoiding coffee, tea and milk while taking iron supplements. The using oral iron preparations 3 times a week instead of daily intake increases the blood iron level in a shorter time.

b) Intravenous iron therapy

Intravenous iron form may be preferred in those who have severe anemia and whose iron level does not increase with oral treatment in the third trimester of pregnancy and/or cannot tolerate oral iron. It is not preferred because there are not enough safety data for first trimester use. It

is more effective than oral iron preparations and has less gastrointestinal side effects .

Indications

- Can not tolerate oral iron preparation
- Not increasing iron levels despite treatment
- Increasing iron level in a short time for pregnant women
- People who have had stomach and intestinal surgery, which has adverse effects on iron absorption

7. Evaluation of response to treatment

An increase in the number of reticulocytes is observed in the first week after iron replacement. An increase in hemoglobin level of at least 1g/dL is observed within about 2 to 3 weeks.

Hemoglobin level is checked within 2-3 weeks after oral iron therapy and oral iron tolerability is checked. If oral iron tolerance and increase in hemoglobin level are as expected, treatment continued throughout pregnancy and postpartum period. If the expected response and tolerance are not good, intravenous iron therapy should be considered.

8. Duration and frequency of follow-up

By the Ministry of Health in our country;

- For iron support; at least 3 follow-up during pregnancy, at least 1 follow-up postpartum
- Once a month for moderate anemia
- In severe anemia, the first follow-up is two weeks later, subsequent follow-ups once a month.

9. Iron use side effects

In order to increase tolerance, extending the time between doses, switching to a fluid that can be titrated more easily, or switching to intravenous iron (if in the second or third trimester) can be counted (9).

a) Side effects of intravenous iron therapy:

A meta-analysis on the safety of intravenous iron treatment revealed no increased risk for serious adverse effects, mortality and infection (10). Side effects such as fever, arthralgia, myalgia often heal spontaneously without intervention. It should be preferred as an alternative to erythrocyte transfusion in severe anemic cases, where there is no response to parenteral iron treatment or in cases where rapid correction is desired.

b) Drugs and foods that disrupt iron absorption:

- Anticonvulsants
- Sulfonamides
- Antacids
- Calcium-containing foods
- Tea, coffee, spinach, beets, soy products, phytat in bran and grains.

*Consumption with foods rich in vitamin C (orange juice) and acidic foods, and be consumed before eating increase the absorption of iron drugs.

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