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A REVEW ON RECENT ADVANCE IN DIAGNOSIS AND TREATMENT OF ISCHEMIC HEART DISEASE

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ABSTRACT

Ischemic heart disease is a pathological condition characterized by reduced cardiac blood flow that causes a mismatch between myocardial oxygen supply and demand. Heart disease therapy advances are rarely attributed to a single year. Rather, they reflect small chunks of knowledge gathered over a long period of time. While the treatment of cardiovascular illness is always evolving, the usefulness of certain advancements has been well established enough to deserve consideration in this summary. In recent years, a reassuring number of successful methods for treating cardiac disease have been developed, indicating actual progress. The current study focuses on the epidemiology, etiology, symptoms, acute coronary syndrome, and ischemic heart disease diagnosis.

KEYWORDS: Ischemic heart disease, review, Diagnosis, Treatment.

INTRODUCTION

Ischemic heart disease is a pathological condition characterized by reduced cardiac blood flow that causes a mismatch between myocardial oxygen supply and demand. The underlying pathological process is most frequently coronary artery disease (CAD), due to atherosclerotic obstruction or spasm of the epicardial coronary arteries, or microvascular dysfunction. Hence, ischemic heart disease and CAD are terminologically often used synonymously. Ischemic heart disease is a chronic, progressive disease but it can at any time translate or even initiate as an unstable condition, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. The dynamic nature of the CAD process results in a variety of clinical

presentations, which can most simply be categorized as chronic coronary syndromes (CCS) or acute coronary syndromes (ACS).

The term CCS was introduced in the 2019 ESC guidelines.[1] In former guidelines[2] and in the American guidelines[3,4] the terms stable ischemic heart disease or stable coronary heart disease have been used. ACS includes unstable angina pectoris and acute myocardial infarction, further divided up into ST-segment elevation myocardial infarction (STEMI) and non-STsegment elevation myocardial infarction (NSTEMI).

Epidemiology

Even though the mortality from cardiovascular disease is decreasing, it remains the most common cause of death worldwide. In Europe CAD causes more than 1.7 million deaths annually, accounting for 20% of all deaths, 7 and in the US accounting for about 30% of all deaths over 35 years. Age standardized death rates for CAD have declined by 30%-60% in high-income and many middle-income countries over the last 10 years. There are still major differences in the burden of cardiovascular disease between countries. In Europe the highest mortality rates from CAD are found in non-EU member countries and the lowest in EU-15 countries.[5]

One-year mortality after STEMI varies in the national registries for European countries between 4% and 12%.Based on people reporting heart or circulation symptoms the prevalence of CAD in Europe in 2014 was 9.2%, and similarly in the US. The prevalence and the given risk of CAD in a population have declined over the last decades. Earlier pretest probability tables were based on data from Diamond and Forrester[6] and were updated in the 2013 ESC guidelines(2) based on data from Genders et al. 12 Since then, observational studies have demonstrated that the prevalence of obstructive CAD in a population suspected of CAD is lower than expected from previous pretest probability models. As a consequence, new pretest probability models have been presented in 2019 ESC guidelines. The updated pretest probability will have an impact on the number of invasive and noninvasive tests in patients suspected for CCS and impact when a given test can rule-in or rule-out CCS.

Pathogenesis

Atherosclerosis is a multifactorial, immunoinflammatory disease of the arteries driven by lipids. Risk factors, such as smoking, hypertension, diabetes mellitus, male gender and inflammation accelerate the process where lipids enter the intima and atherosclerotic plaque

develop in the coronary arteries.[8] Reduced blood flow in the coronary arteries due to atherosclerotic luminal narrowing and endothelial dysfunction creates an imbalance between oxygen demand and supply in the myocardium causing ischemia. In the event of plaque rupture acute coronary thrombosis may occur and cause partial or complete occlusion of the artery and abrupt hypoperfusion and myocardial infarction.

Nonatherosclerotic causes of myocardial ischemia include primary or induced coronary artery vasospam, impaired microcirculation or arteriolar dysregulation, coronary emboli, decreased coronary perfusion due to hypotension, decreased blood oxygen content, significant increased myocardial oxygen demand (eg, severe aortic stenosis, tachyarrhythmia).

Symptoms

Chronic Coronary Syndrome In the 2019 ESC Guidelines on CCS, nsix clinical scenarios are most frequently encountered among patients with suspected CAD:

(i) 'stable' angina symptoms, and/or dyspnea;
(ii) patients with new onset of heart failure or left ventricular (LV) dysfunction;
(iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS event or patients with recent revascularization;
(iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization;
(v) patients with angina and suspected vasospastic or microvascular disease;
(vi) asymptomatic subjects in whom CAD is detected at screening.

The characteristics of typical and atypical anginal symptoms. The likelihood of CAD increases with typical presentation although presentation is not a specific determinant. Many patients suspected for CCS present atypical or nonanginal symptom characteristics. Patients with obstructive CCS may even be asymptomatic, in particular among patients with diabetes mellitus, or solely manifest as heart failure. Severity of angina is clinically graded by the Canadian Cardiovascular Society classification (CCS-class), where the angina threshold is quantified according to the relation to physical activity intensity.[9]

Acute Coronary Syndrome

ACS covers acute myocardial infarction and unstable angina pectoris. Acute myocardial infarction is defined as myocardial injury and necrosis due to myocardial ischemia with a subsequent elevation in cardiac troponin,[10] while unstable angina pectoris represents the

unstable clinical manifestation of CAD with longer lasting angina pectoris at rest without evidence of necrosis and therefore no elevation of cardiac troponin. Symptoms of ACS are acute onset of angina pectoris that is prolonged ongoing for >20 minutes. Like CCS accompanying symptoms of nausea, fatigue, and dyspnea may occur. Unstable angina pectoris can also present as crescendo angina, that is, worsening of angina in intensity, severity, and activity threshold for onset.

Diagnosis

Diagnosis of CCS The general approach for initial diagnostic management of patients suspected of CCS is based on selecting the most suitable noninvasive functional or noninvasive anatomical test from the given patient's characteristics in order to qualify the risk of obstructive CAD and indication for revascularization. Only if the risk of obstructive CAD is very high or obstructive.

Table 1: Pretest Probability of Obstructive Coronary Artery Disease in Patients According to Symptoms, Age, and Gender.

Age	Typical		Atypical		Non anginal		Dyspnea	
	Men	Women	Men	Women	Men	Women	Men	Women
30-39	3%	5%	4%	3%	1%	1%	0%	3%
40-49	22%	10%	10%	6%	3%	2%	12%	3%
50-59	32%	13%	17%	6%	11%	3%	20%	9%
60-69	44%	16%	26%	11%	22%	6%	27%	14%
+70	52%	27%	34%	19%	24%	10%	32%	12%

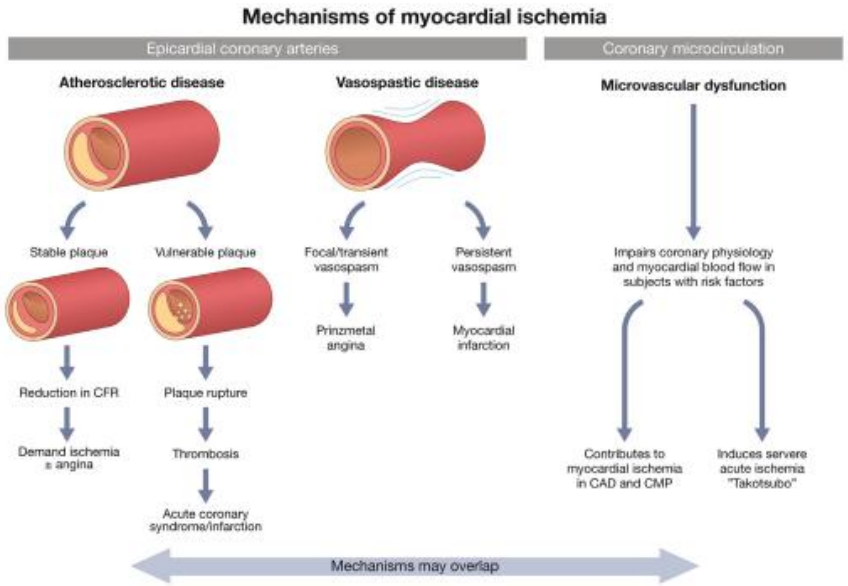

Figure 1: Illustration of pathogenic mechanisms of myocardial ischemia. Atherosclerotic disease, vasospastic disease, and microvascular dysfunction can cause

transient ischemia or acute severe ischemia and infarction. CAD, coronary artery disease; CFR, coronary flow reserve; CMP, cardiomyopathy.

Table 2: The Characteristics of Typical and Atypical Anginal Symptoms.

Typical angina	Meets the following three characteristics: I: Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm II: Provoked by physical exertion, emotional stress, or cold III: Relieved by rest or nitrates within 5 minutes
Atypical angina	Meets two of the characteristics
Nonanginal chest pain	Meets only one or none of the characteristics
Angina equivalent dyspnea	Shortness of breath

The initial diagnostic work-up can be summarized in 5 steps

(1) Assessment of the symptoms and excluding ACS;

(2) Clinical cardiac examination including resting electrocardiogram (ECG) and echocardiography;

(3) Evaluation of coexisting cardiac and medical conditions that may influence the symptoms, the choice of further testing, or potential treatment; and from this;

(4) Evaluate probability and clinical likelihood of CCS; and finally from this;

(5) Decide whether further testing is needed and, if so, decide between noninvasive anatomical test coronary computed tomography angiography (CTA) or noninvasive functional tests including stress ECG, stress echocardiography, single-photon emission computed tomography (SPECT) or positron emission tomography (PET) perfusion imaging, stress cardiac magnetic resonance (CMR) perfusion imaging, or coronary computed tomography angiography derived fractional flow reserve (FFR-CT) for further cardiac imaging and testing.

1. Assessment of symptoms

Patients are evaluated for the presence of ACS and if suspected guidelines for this are followed.[11] The characteristics of the symptoms are evaluated and classified as typical, atypical, or nontypical.

2. and 3. Clinical assessment and evaluation of coexisting cardiac and medical conditions

Full blood count, including hemoglobin, creatinine measurement, lipid profile, HbA1c, and assessment of thyroid function are a Class I recommendation. These parameters may explain

the symptoms, may influence the clinical likelihood of CCS, or influence the cardiac treatment and choice of cardiac imaging and testing.[12]

Resting ECG is import in patients with suspected CCS. Although often normal despite CAD, abnormalities that are predictive of obstructive CAD may be identified and strengthen the clinical likelihood of CAD such as pathological Q-wave in multiple leads, T-wave inversions, and left bundle-branch block. ST-segment depression during supraventricular tachyarrhythmia is not predictive of obstructive CAD.[13]

4. Assessment of pretest probability and clinical likelihood of coronary artery disease

From patient characteristics, including gender, age, and symptom characteristics a pretest probability of obstructive CAD can be calculated. Studies have shown that in patients classified with pretest probability <15% the annual risk of cardiovascular death or myocardial infarction is <1%. Patients with pretest probability <5% should rarely undergo further diagnostic testing, while pretest probability >15% indicates a need for further testing. Especially when pretest probability is between 5-15% further improvement of the pretest probability assessment can be obtained by evaluating the clinical likelihood. This is done by incorporating information on risk factors for CAD, as family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other lifestyle factors, ECG abnormalities, and LV dysfunction on echocardiography.

Deciding on diagnostic testing

In patients with pretest probability >15% or pretest probability between 5-15% in whom the clinical assessment increases the clinical likelihood of obstructive CAD a noninvasive test should be performed.

Functional imaging with PET or SPECT perfusion imaging, stress CMR perfusion imaging for myocardial ischemia are used as first-line test in some places due to local availability but mainly recommended, when coronary CTA has shown CAD of uncertain functional significance or if not diagnostic, and in patients with very high pretest probability or clinical likelihood of obstructive CAD, for example patients with known CAD, particularly if the patient has undergone previous percutaneous coronary intervention (PCI). For many years ECG exercise test was the most commonly used first-line diagnostic test despite its very poor sensitivity and low specificity. The main reason was its worldwide availability and low risk.

While ECG exercise test still predominates in the AHA/ACC guidelines it has been downgraded in the 2019 ESC guidelines.

Diagnosis of ACS

Acute myocardial infarction is diagnosed by the presence of elevation of cardiac troponin values, and at least one of the following: symptoms compatible with angina, new ischemic ECG changes, development of pathological Q-wave in ECG, imaging evidence of new loss or reduced function of viable myocardium, or identification of coronary thrombus by ICA. Unstable angina pectoris is diagnosed as the same clinical presentation as ACS but with no troponin elevation.

Treatment of Ischemic heart disease

Regenerative approach

Msc Differentiation

MSCs are a subset of bone marrow cells that can be isolated from other bone marrow derived mononuclear cells (BM-MNCs) by their rapid adherence to plastic tissue culture dishes. Following culture, the remaining cells typically express markers CD29 (integrin ß-1), CD44 (hCAM), CD90 (thy-1), CD105, and CD117 (c-kit) and are negative for the hematopoietic and vascular markers CD34, CD45, and CD11b.[14]

Using growth-factor rich selective media, MSCs have been shown to be able to differentiate into multiple mesoderm lineages and differentiated cell types, including osteoblasts, adipocytes, skeletal muscle myocytes/myotubes, pancreatic islet cells, and cardiomyocytes. If delivered in vivo, they have been shown to engraft and transdifferentiate into cardiomyocytes, repairing the infarcted myocardium.[15]

Paracrine effect

MSCs also secrete multiple cytokines and growth factors, together termed their “secretome,” which contribute to their paracrine therapeutic effect. These factors are released in soluble form, or in exosomes and in extracellular vesicles (EVs), and can be sampled by collecting the medium in which the cells are cultured, so-called “conditioned medium” (CM).[16] Over 30 systematic proteomic studies on MSC CM have been conducted, reporting a multitude of growth factors that could have potent paracrine effects. These include hepatocyte growth factor (HGF), interleukin-1 (IL1) and 26 (IL6), stem-cell derived factor-1 (SDF-1), and several others. Within the EVs or exosomes, several mRNAs have been found, such as

miR221 and miR-19a, which are involved with suppressing apoptosis or stimulating Akt (a potent survival mediator) in various cell types.[17]

EVS and exosomes

The use of EVs and exosomes, without the cells themselves, is a growing practice for regenerative therapy. EVs have a size between 100 nm and 1 mm and derive from the detachment of cytoplasmic protrusions. EVs from MSCs express CD13, CD29, CD44, CD73, and CD105, similar to MSCs themselves.[18]

Exosomes have a size ranging between 30 and 100 nm and originate from fusion of endosomes with the plasma membrane, which are released by exocytosis. Both contain nucleic acids, coding mRNA and noncoding RNA. Coding mRNAs present in EVs include transcripts related to control of transcription, cell proliferation, and immune regulation.[19] Among the noncoding RNAs contained in released MSC-EVs, there are selected patterns of miRNAs, which can be transferred to target cells and downregulate mRNA translation and protein expression. Recent studies suggest that the therapeutic effect of MSCs is in large part due to secreted EVs and exosomes.[20]

Clinical trials of mscs for ischemic heart disease

While most cell therapy trials for ischemic heart disease (IHD) have concentrated on BM-MNCs, isolated MSCs have also been used in trials of acute and chronic IHD. Table 1 summarizes these studies. Chen et al.[21] randomized 69 patients after acute MI and injected 48–60 3 109 MSCs into the infarct related coronary artery 10 days following reperfusion and stenting. At 3 and 6 months follow-up, they found a significant difference in the improvement of left ventricular ejection fraction (LVEF) in the MSC group compared to placebo (17% vs. 5%), in addition to reduced infarct size.[22]

Fatty acid metabolism in the setting of ischemia

Circulating fatty acid levels increase after an acute myocardial infarction or during cardiac surgery, such that during and after ischemia the heart muscle can be exposed to very high concentrations of fatty acids.[23]

The detrimental effects of high plasma fatty acid levels on mechanical and electrophysiologic characteristics of the heart after ischemia reperfusion has been recognized for 20 years. High plasma fatty acid concentrations have also been shown to increase the severity of ischemic

damage in a number of different experimental animal models of cardiac ischemia, and has also been linked to a depression of mechanical function during aerobic reperfusion of previously ischemic hearts. During reperfusion of the heart after ischemia, fatty acid oxidation can quickly recover and dominate as the source of ATP production. These high rates of fatty acid oxidation contribute to a marked decrease in cardiac efficiency during reperfusion. However, if glucose oxidation is stimulated during reperfusion, a significant increase in cardiac efficiency results, with a parallel improvement in cardiac function.[24]

Pharmacologic stimulation of Glucose oxidation

Another approach to decreasing the detrimental effects of fatty acids is to directly modify energy preference in the heart. One strategy to stimulate myocardial glucose metabolism is to directly stimulate the rate-limiting enzyme for glucose oxidation—the pyruvate dehydrogenase complex. An agent that effectively does this is dichloroacetate, which by increasing the amount of pyruvate dehydrogenase in the active form will markedly stimulate glucose oxidation. In experimental studies, dichloroacetate has been shown to dramatically improve recovery of mechanical function after ischemia.[25]

Clinical efficacy of dichloroacetate as an anti-ischemic agent has also been shown. In patients with coronary artery disease, dichloroacetate has been shown to increase left ventricular stroke volume. Unfortunately, whereas dichloroacetate is very efficacious as a stimulator of glucose oxidation, it is not a particularly potent drug, and blood levels of dichloroacetate need to approach millimolar levels to increase myocardial glucose oxidation. Another limitation of this agent is its short half-life after either oral or intravenous administration.[26]

Trimetazidine Effects on Glucose Metabolism

Trimetazidine is a novel agent that has anti-ischemic properties that can occur independently of hemodynamic changes. Like ranolazine, trimetazidine also belongs to a piperazine group of compounds and is structurally similar to ranolazine. Trimetazidine has now been licensed in a number of countries as a cellular anti-ischemic agent for the treatment of angina. Experimentally, trimetazidine has been shown to decrease ST segment elevation during coronary artery occlusion of rabbit hearts, and is cardioprotective in in vitro models of ischemia. Clinically, double-blind crossover trials have shown that trimetazidine is as effective as nifedipine for treatment of stable angina.[27]

Antithrombotic Therapy

Antiplatelet therapy reduces the risk of serious vascular events as myocardial infarction, stroke, and vascular death in moderate to high-risk patient at an increased risk of bleeding. In patients with previous myocardial infarction or revascularization the beneficial effect of low dose aspirin 75- 100 mg daily substantially exceeds the bleeding risks and is a Class I, Level A recommendation.[4]

Antianginal Therapy

Short-acting nitroglycerin sublingual is the cornerstone of acute symptom relief from angina. Antianginal medications that reduce and prevent angina symptoms include betablockers, calcium channel blockers, and long-acting nitrates. In symptomatic patients with reduced ejection fraction betablockers are indicated as they reduce mortality and morbidity. Beta-blockers and calcium channel blockers effectively reduce symptoms but have not been shown to improve patient outcome in CCS patients without heart failure or prior myocardial infarction.[28]

Cardiovascular Risk Factor Modification

Lowering low-density lipoprotein (LDL) with statins has a major effect on cardiovascular events and death. All-cause mortality is reduced by 10% per 1.0 mmol/L LDL reduction regardless of any baseline threshold. For many years European and American guidelines have recommended LDL lowering to <1.8 mmol/L or at least a 50% reduction, when the baseline LDL level is 1.8-3.5 mmol/L. 4.

Revascularization in CCS

While optimal medical therapy is crucial for reducing symptoms, counteracting progression of atherosclerosis, and preventing atherothrombotic events, myocardial revascularization has a central role in the management of CCS as an adjunct to medical therapy. The two objectives of revascularization are symptom relief in patients with angina and/or improvement of prognosis.

Revascularization in ACS

In ACS patients immediate revascularization of the culprit lesion is recommended in STEMI patients with symptoms <12 hours while in NSTEMI patients revascularization is recommended within 48 hours. Nonculprit lesions should be treated by FFR-guided revascularization.[29]

CONCLUSION

Myocardial ischemia, in our opinion, is caused by a breakdown in the crosstalk between myocardial energy status and coronary blood flow. The complicated aetiology of myocardial ischemia may include more than only coronary macrovascular and microvascular dysfunction. More evidence is needed to have a better understanding of the underlying causes of IHD, which nearly always occur in the most distal and microscopic parts of the coronary tree.

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