

Ischemic Cardiopathy and Diagnostic Methods for Early Diagnosis

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ABSTRACT

Cardiovascular disease is the leading cause of death around the world. It's still responsible of over 4 million deaths/year, close to half of all deaths in Europe. Cardiovascular disease is a group of diseases that include coronary heart disease and coronary artery disease. The mortality for coronary heart disease has gradually declined over the last decades in western countries thanks to the knowledge of cardiovascular risk factors and of pathophysiological mechanisms underlying ischemic heart disease that has enable primary prevention and new clinical and therapeutic approaches. The international guidelines recommend a stepwise approach for decision making in patients with suspected coronary artery disease. The process begins with the determination of pre-test probability and is followed by invasive or non-invasive diagnostic tests in patients with an intermediate probability of disease. The aim of this article is give a general view of first and second line non invasive diagnostic test for the early diagnosis of coronary artery disease.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death among Europeans and around the world [1]. It's still responsible of over 4 million deaths/year, close to half of all deaths in Europe (Table 1). The proportion of all deaths that are attributable to CVD is more in women (51%), less in men (42%). CVD is a group of diseases that include both the heart and blood vessels, therewith including coronary heart disease (CHD) and coronary artery disease (CAD), and acute coronary syndrome (ACS) among several other conditions. ACS is a subcategory of CAD, while CHD results of CAD. CHD regards about 1.8 million deaths, 20% of all deaths in Europe annually, about one-third of all deaths in people older than 35 years [2]. Luckily the mortality for CHD has gradually declined over the last decades in western countries thanks to primary prevention and new clinical and therapeutic approaches (Figure 1). Estimation of true prevalence of CHD in the population is complex. This estimation is often performed through population surveys. In particular, the survey estimated that about 15.4 million persons older than 20 years in the United States have ischemic heart disease. Despite the prevalence of CHD is higher in men that in women, the latest trends show a decrease in prevalence in men and an increase in prevalence in women maybe because cardiovascular risk factors are not well identified and treated in women [3].

Table 1: Number and percentage of death drom cardiovascular disease in Europe [1].

	Cardiovascular disease(total)		Coronary heart disease		Cerebrovascular disease		Other Cardiovascular disease	
Males								
Total deaths (all ages)	1862774	42%	876017	20%	429756	10%	557001	12%
Premature deaths-before age 75	939698	36%	473501	18%	201780	8%	264417	10%
Premature deaths-before age 65	508132	31%	253432	16%	95249	6%	159451	10%
Females								
Total deaths (all ages)	2219326	51%	903330	21%	627227	14%	688769	16%
Premature deaths-before age 75	536712	37%	232683	16%	155702	11%	148327	10%
Premature deaths-before age 65	201492	27%	77166	10%	54470	7%	69856	9%
Total								
Total deaths (all ages)	4082100	46%	1779347	20%	1056983	12%	1245770	14%
Premature deaths-before age 75	1476410	37%	706184	18%	357482	9%	412744	10%
Premature deaths-before age 65	709624	30%	330598	14%	149719	6%	229307	10%

Cardiovascular disease in Europe: Epidemiological update. Eur. Heart J. 2013; 3028-3034.

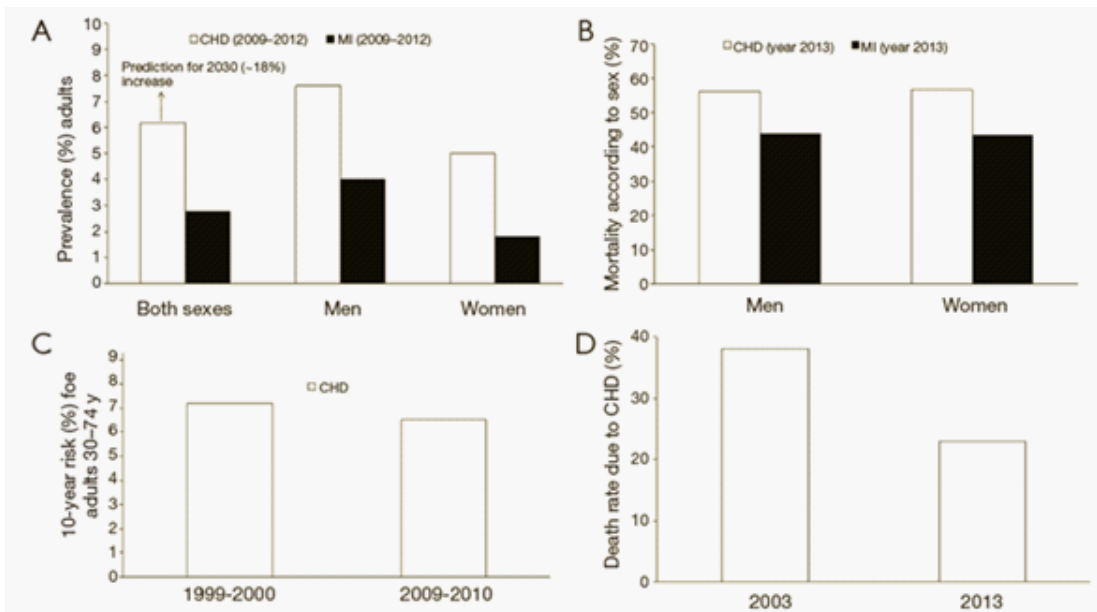


Figure 1: Reduction of mortality in last decades in USA [3].

Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. *Circulation* 2016;133:447-454.

The reduction of global mortality is due to the knowledge of cardiovascular risk factors and of pathophysiological mechanisms underlying ischemic heart disease. This has enabled the development of various diagnostic techniques and provocative tests to stratify the risk or to unmask the disease early in order to treat the patients before the possible consequences of coronary heart disease.

PHYSIOPATHOLOGY

Atherosclerosis is an immune-inflammatory disease caused by lipids. It is a progressive, systemic disease that involves the wall of the blood vessels that consists of three layers: the intima (the inner layer of the vessel wall and is formed by endothelial cells immersed in an extracellular matrix), the average (smooth muscle cells, collagen fibers and elastic fibers, also immersed in the extracellular matrix) and the advent (most exterior layer and is made of dense fibro elastic tissue, nutritive vessels and nerve fibers). Atherosclerosis causes a stiffening of the vascular walls for the progressive replacement of smooth muscle cells with connective fibrous tissue. This kind of manifestation is dominant in small caliber arteries, in medium and large caliber arteries, we can also find the atheromatosis, appearance of cholesterol-infiltrating lesions. The clinical manifestation of atherosclerosis can be different depending on the vascular bed involved or on its onset, acute or chronic [4]. Previously considered a cholesterol storage disease, we currently

understand atherogenesis as a complex interaction of risk factors including cells of the artery wall and the blood and molecular messages that they exchange [5]. Inflammation [6] also participates in the local, myocardial, and systemic complications of atherosclerosis. In fact when the arterial endothelium encounters certain bacterial products or risk factors as diverse as dyslipidemia, vasoconstrictor hormones in hypertension, the products of glycooxidation associated with hyperglycemia, or pro inflammatory cytokines derived from excess adipose tissue, these cells augment the expression of adhesion molecules that promote the sticking of blood leukocytes to the inner surface of the arterial wall. The consequence of the inflammatory barm underway in the early atheroma, smooth muscle cells migrate from the tunica media into the intima. These cells proliferate and elaborate a rich and complex extracellular matrix and, together with endothelial cells and monocytes, they secrete matrix metalloproteinases (**MMPs**) in response to various oxidative, hemodynamic, inflammatory, and autoimmune signals. MMPs, in balance with their endogenous tissue inhibitors, modulate numerous functions of vascular cells, including activation, proliferation, migration, and cell death, as well as new vessel formation, geometric remodeling, healing, or destruction of extracellular matrix of arteries and the myocardium. Certain constituents of the extracellular matrix (notably proteoglycans) bind lipoproteins, prolong their residence in the intima, and render them more susceptible to oxidative modification and glycation. These products of lipoprotein modification, including oxidized phospholipids [7] and advanced glycation end products, sustain and propagate the inflammatory response. In addition to proliferation, cell death (including apoptosis) commonly occurs in the established atherosclerotic lesion. The death of lipid-laden macrophages can lead to extracellular deposition of tissue facto. The extracellular lipid that accumulates in the intima can coalesce and form the classic, lipid-rich “necrotic” core of the atherosclerotic plaque. These plaques are also called atheromatous plaques or simply atheromas they cause a thickening of the arterial wall and a narrowing of the arterial space through which blood flows to reach the heart. Coronary atherosclerotic plaques are therefore characterized by extreme structural and biological heterogeneity; we define as *vulnerable* the atherosclerotic plaque that has a greater risk of developing thrombosis. Remarkable efforts have been made to recognize the most vulnerable plaques. The underlying mechanisms of coronary thrombosis are rupture (in 85% of cases) and erosion. In retrospective autopsy studies, histologic features were more commonly observed in plaques thought to be responsible for most acute coronary events compared with stable plaques: a larger lipid core (40% of total lesion area), a thinner fibrous cap (<100 µm), and more inflammatory cells (about 26% macrophage infiltration of fibrous cap compared with 3% in stable plaques) [8-10]. The minor criteria for plaque vulnerability included the presence of superficial calcified nodules; yellow color, which may indicate a larger lipid core; intraplaque hemorrhage; endothelial dysfunction (impaired endothelial vasodilator function); and expansive (positive) remodeling, which refers to compensatory outward enlargement of the vessel wall without luminal compromise [11]. The size of a plaque or the severity of stenosis provides little information about the vulnerability of the plaque itself. Many plaques prone to breakage are negligible in coronary angiography due to the remodeling of the vessel. The

plaques responsible for an acute coronary syndrome are usually large and associated with a compensatory increase in the arterial vessel that tends to maintain normal outward remodeling. Indeed, many studies have shown that the culprit lesion in about two-thirds of patients occupies less than 70% of the vessel's lumen. Plaques, which are responsible for stable angina, are smaller in size, but cause a shrinkage of major limbs due to inward remodeling. Clinical observations also show that acute coronary syndrome responsible lesions are less calcific than plaque-responsible plaques suggesting that calcium gives plaque stability. Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand or supply mismatch, related to ischaemia, which are usually inducible by exercise, emotion or other stress and reproducible but, which may also be occurring spontaneously. Such episodes of ischaemia are commonly associated with transient chest discomfort (angina pectoris).

EXERCISE TEST

Introduction

The international guidelines recommend a stepwise approach for decision making in patients with suspected stable coronary artery disease. The process begins with the determination of pre-test probability and is followed by non-invasive diagnostic tests in patients with an intermediate (15-65%) probability of disease. The pre-test probability is influenced by the prevalence of the disease in the population studied and by clinical features such as: presence of cardiovascular risk factors, age, gender and the nature of symptoms. No testing is recommended in patients with low ($\leq 15\%$) or high ($\geq 85\%$) pre-test probability (Table 2) [12]. Because of its simplicity and widespread availability, exercise test is a first line test for the diagnostic and prognostic evaluation in patients with suspected or known stable coronary artery disease. Exercise testing is generally a safe procedure but both myocardial infarction and death have been reported [13], so a precise clinical evaluation of the indications and contraindications is required [14] (Table3).

Table 2: Clinical pre-test probabilities in patients with stable chest pain symptoms [12].

Age	Typical angina		Atypical angina		Non-anginal Plan	
	Men	Women	Men	Women	Men	Women
30-39	59	28	29	10	18	5
40-49	69	37	38	14	25	8
50-59	77	47	49	20	34	12
60-69	84	58	59	28	44	17
70-79	89	68	69	37	54	24
> 80	93	76	78	47	65	32

ECG = Electrocardiogram; PTP = Pre-test portability; SCAD = Stable coronary artery disease.

Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur. Heart J.* 2013; 34: 2949-3003.

Table 3: Contra-indications to Exercise Test.

Absolute	
-	Acute myocardial infarction (within 2 days)
-	Unstable angina
-	Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
-	Severe aortic stenosis
-	Uncontrolled symptomatic heart failure
-	Acute pulmonary embolus or pulmonary infarction
-	Acute myocarditis or pericarditis
-	Acute aortic dissection
Relative	
-	Left main coronary stenosis
-	Moderate stenotic valvular heart disease
-	Electrolyte abnormalities
-	Severe arterial hypertension‡
-	Tachyarrhythmias or bradyarrhythmias
-	Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
-	Mental or physical impairment leading to inability to exercise Adequately
-	High-degree atrioventricular block

Exercise Testing Procedure

Patient education is considered as a good clinical practice in order to obtain maximum cooperation, the patient must be on fasting and appropriate physical exercise clothing. Exercise test can be performed by a trained nurse with the supervision of a physician, who should be in the immediate vicinity and available for emergencies. Clinical history and examination, blood pressure measurement and baseline ECG are an integral part of the test. The exercise test can be performed by treadmill or bicycle. The bicycle (most common in Europe) makes it possible to perform stress in the sitting position with a lower mobility of the trunk that allows greater stability of the electrocardiographic trace and a more accurate measurement of the blood pressure. On the other and, the fatigue of the quadriceps muscles in patients who are not experienced cyclists is a major limitation, because subjects usually stop before reaching their maximum oxygen uptake. The treadmill stress test (most common in North America) allows for a more natural exercise and achieving a higher oxygen uptake for the contemporary engagement of a mayor number of muscles. The disadvantages are an increased risk of accidents and the difficulty of blood pressure and ECG monitoring. The exercise test protocols, both cycle and treadmill, should be preceded by an initial warm up phase for 1 or 3 min and followed by an adequate recovery phase of at least 5 min at reduced working load. The protocols are set up to allow the patient to keep operating times between 6 and 12 minutes. The cyclo-ergometer test is carried out with an increase in variable working loads of 5 or 25 W per 1 or 2 min. There are numerous executive

protocols for the treadmill- exercise test, but the major one used is the modified Bruce protocol with gradual increase in speed and inclination every 3 minutes. Generally, the test stops at 85% of the maximum theoretical heart rate (**HR**) (predicted according to the formula: $HR_{max} = 220 - \text{age}$) but there are numerous other indications on the interruption of the test such as: subject's desire to stop (fatigue, leg cramps), appearance of chest pain associated with significant ECG, safety reasons (drop in systolic blood pressure from baseline blood pressure despite an increase in work load, signs of poor perfusion such as cyanosis or pallor, sustained ventricular tachycardia, ST depression ≥ 2 mm, other arrhythmias, including supra ventricular tachycardia or bradyarrhythmias, development of bundle branch block).

Interpretation of the Exercise Test

Interpretation of the exercise test should include exercise capacity and clinical, hemodynamic and electrocardiographic parameters. Exercise capacity has great prognostic significance having proved to be the most powerful predictor of death from any cause. A good exercise ability reflects the integrity of the cardiopulmonary system and is the indicator of an active lifestyle. Theoretically, functional capacity should be measured by analyzing the consumption of oxygen during exercise by expanding gases collected or by measuring the actual work produced, but this is difficult to apply in clinical practice so it is evaluated indirectly either by the operating time or through METS (multiples of basal metabolic consumption, in absolute rest). The value of the METS associated with a given exercise is derived from the workload that the subject manages to undertake, so at each stage of any protocol correspond a given METS value. METS is useful for comparing the exercise capacity of tests performed with different protocols. The hemodynamic parameters during ergo metric testing undergo normal physiological changes induced by stress. Any abnormal HR and arterial blood pressure (**BP**) during the test and recovery phase have a negative prognostic value and can also be sign of coronary heart disease. HR changes during exercise and during the post-exercise recovery period are due to a balance between the activity of sympathetic and vagal systems. Cronotrope incompetence is defined as an attenuated HR response to exercise. The inability to reach 85% of HR max can be used as an index of cronotropic incompetence. It is associated with an increased severity of myocardial ischemia. During the exercise test, BP should be measured every 2 minutes and whenever signs or symptoms occur. Normally systolic BP tends to increase by 5-10 mmHg for each sustained MET; in an average age patient with an average stress tolerance we expect an increase of 40-60 mmHg, reaching a peak of 160-200 mmHg. Diastolic blood pressure (**DBP**) generally remains unchanged or may be slightly elevated or lowered. During the recovery phase the systolic blood pressure (**SBP**) should normalize within 6 min and it can also drop to lower baseline values for a few hours. Hypertensive response: SBP values of ≥ 200 mmHg in men or ≥ 190 mmHg in women, DBP ≥ 90 or an increase of more than 10 mmHg compared to the basal values. There are conflicting data on the topic, some authors have shown a significant increase in cardiovascular events in patients with hypertensive response, other ones have shown a decrease of risk. Hypotensive response to stress is defined by

one of the following situations: a lack of SBP increase of at least 20-30 mmHg, a decrease of SBP after an initial increase; a decrease in SBP below the resting value. Hypotensive response to stress may be associated with severe myocardial ischemia, cardiomyopathy, arrhythmias, ventricular effusion obstructions, vasovagal reactions, hypovolemia or iatrogenic effects. In the absence of electrocardiographic symptoms or signs of ischemia, the stress hypotension does not associate with increased risk of future cardiac events.

The analysis of the ECG is a fundamental moment for the interpretation of the exercise test. The main diagnostic ECG abnormality during ECG exercise testing consists of a horizontal or down-sloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06-0.08s after the J-point, in one or more ECG leads. It is worth noting that, in about 15% of patients, diagnostic ST-segment changes appear only during the recovery phase [12]. In addition to considering the ischemic alterations of the ST section, it is important to verify the occurrence of any arrhythmias whose appearance is favored by the increase in circulating catecholamines, metabolic and a possible stress-induced myocardial ischaemia. The presence of isolated ectopic ventricular beats during the execution of exercise test is a frequent and non-pathological finding that increases with the age of the patient. In itself, ventricular extras are not dangerous unless they occur in patients with sudden death history, valvulopathy, cardiomyopathy or severe ischemia. Ventricular arrhythmias are not an ischemic heart failure marker in the absence of pathological changes in the ST segment. However, they are an indication of increased risk of future cardiac events if they appear in patients with recent myocardial infarction [15].

Influence of Other Factors on Test Performance

To obtain maximal diagnostic information, exercise testing should be performed without the influence of any drugs. Digoxin produces abnormal exercise induced ST depression in 25-40% of normal subjects. The prevalence of abnormal responses is directly related to age. Although patients must be off the medication for at least 2 weeks for its effect to be gone, it is not necessary to do so before diagnostic testing. β -Blockers have a marked effect on maximal exercise heart rate, so exercise test may have reduced diagnostic value. Other drugs, including antihypertensive agents and vasodilators, can affect test performance by altering the hemodynamic response of blood pressure. Acute administration of nitrates can attenuate the angina and ST depression associated with myocardial ischemia. Flecainide has been associated with exercise-induced ventricular tachycardia.

Exercise test value is also influenced by the presence of stable electrocardiographic abnormalities, such as: presence of left branch block, paced rhythm and Wolff-Parkinson-White syndrome, in which cases the ECG changes are not interpretable. Additionally, false positive results are more frequent in patients with abnormal resting ECG in the presence of left ventricular hypertrophy, electrolyte imbalance, intra ventricular conduction abnormalities, a trial fibrillation [16-18]. Exercise ECG testing is also less sensitive and specific in women [12].

The goal of a physician conducting a diagnostic test is to determine, the post-test probability or the probability that the patient has the disease or not. According to the Bayes theorem, the post-test probability is determined by the product between the probability of pre-test disease and the probability that the test will provide real results (predictive accuracy). In this important operation, physician can use a number of score that are more reliable in the opinion of cardiologists in diagnosing disease and predicting the patient's prognosis. Based on these results, it is advisable to hold this kind of attitude:

- Patients with low probability of illness/low risk: they have a good prognosis and can be followed over time without taking further tests in the immediate future;
- Patients with a intermediate probability of disease: it is possible taking further imaging tests such as myocardial scintigraphy, checking the adequacy of ongoing therapy, follow the patient with careful follow-up;
- Patients with high probability of illness/high risk: they should be candidates for more aggressive findings (such as coronary angiography) [15].

Stress Echocardiography

Stress echocardiography is the combination of 2D echocardiography with a physical, pharmacological, or electrical stress.

Eco stress is based on three lines of evidence: biochemical, pathophysiologic and clinical. At biochemical level, oxygen deficiency early compromises actomyosin activation, which is indispensable for contraction; at regional level the regional contractility dysfunction is directly related to the decrease in the regional flow and thus provides a sensitive index of regional ischemia; at clinical level, regional alterations of left ventricular mechanics can be easily documented with 2-D echocardiography. The concept of coronary reserve can be used to describe the effects of various physiological and pathological conditions on coronary circulation. Coronary blood flow increases in response to various stimuli (transient coronary occlusion, muscular exercise, injection of vasodilators or a contrast agent). When vasodilatation is at its zenith, the increase in coronary blood flow above its resting level (basal) is termed the 'coronary vascular reserve'.

Physiologically myocardial function is a dynamic and heterogeneous parameter at various levels, and within the same segment, in the various layers. The systolic thickening of the left ventricular wall is approximately 67% in the inner half of the wall (subendocardium) and therefore the subepicardium contributes to a minimum to the overall thickening. This heterogeneity is reflected on perfusion, coronary flow is greater in the subendocardium than the subepicardium and it tends to be slightly higher in the apical respect to the base segments. A strong association between myocardial oxygen consumption and coronary flow is evident not only in physiological conditions (perfect correlation between demand and supply of O_2), but also in pathological conditions that cause an imbalance between these two parameters.

Whichever situation determines ischemia, it is possible to identify a sequence of events: the “ischemic cascade”. The heterogeneity of perfusion is the basis of ischemia, that is the prelude to the onset of alterations in heart metabolism and dysfunction of the diastolic function of the left ventricle followed by regional dis-akinesia and only late, by ECG and symptoms changes

The diagnostic endpoint of the stress echocardiography is the detection of myocardial ischaemia. The three most commonly used stressors are exercise, dobutamine, and dipyridamole. Exercise provides a more physiological environment than pharmacological tests and provides additional physiological data, such as exercise time and workload, as well as information about changes in heart rate, blood pressure and ECG. However, out of five patients, one cannot exercise, one exercises sub maximally, and one has an uninterpretable ECG. Thus, it becomes necessary the use of an exercise-independent approach. Pharmacologic stressors minimize factors such as hyperventilation, tachycardia, hyper contraction of normal walls, and excessive chest wall move-ment, which render the ultrasonic examination difficult during exercise. Dipyridamole and dobutamine act on different receptor populations and induce ischaemia through different haemodynamic mechanisms: dobutamine stimulates adrenoreceptors, increases myocardial oxygen demand, while dipyridamole (which accumulates endogenous adenosine) stimulates adenosine receptors and mainly decreases sub-endocardial flow supply [19,20].

The choice of one test over the other depends on patient characteristics, local drug cost, and the physician’s preference. For instance, a patient with severe hypertension and/or a history of significant atrial or ventricular arrhythmias can more reasonably undergo the dipyridamole stress test, which has no arrhythmogenic or hypertensive effect. In contrast, a patient with severe conduction disturbances, advanced asthmatic disease or under the effect of caffeine should undergo the dobutamine stress test, since adenosine has a negative chronotropic and dromotropic effect, as well as a documented bronchoconstrictor activity.

The examination is carried out starting with ECG monitoring, measurement of BP at rest and the first images are captured using the echocardiographic probe (2,3,4 and 5 chamber projections) to evaluate heart movement under basal conditions and stored time, these images will serve as a comparison during “stress” moments

All stress echocardiographic diagnoses can be easily summarized into equations centred on regional wall function describing the fundamental response patterns as: normal, ischaemic, viable- and necrotic myocardium.

- Normal response: a segment is normokinetic at rest and normal or hyperkinetic during stress.
- Ischaemic response: a segment worsens its function during stress from normokinesis to hypokinesis, akinesis, or dyskinesis (usually at least two adjacent segments for test positivity are required).
- Necrotic response: a segment with resting dysfunction remains fixed during stress.

- Viability response: a segment with resting dysfunction may show either a sustained improvement during stress indicating a non-jeopardized myocardium (stunned) or improve during early stress with subsequent deterioration at peak (biphasic response). This response would indicate a jeopardized region (hibernating myocardium) often improving after revascularization.

A resting akinesis which becomes dyskinesia during stress usually reflects a purely passive, mechanical consequence of increased intra ventricular pressure developed by normally contracting walls and should not be considered a true active ischaemia.

In recent years the evaluation of coronary flow reserve by combining trans thoracic Doppler assessment of coronary flow velocities with vasodilator stress has entered the echo lab as an effective modality for diagnostic and prognostic purposes.

The use of coronary flow reserve as a stand-alone diagnostic criterion suffers from two main limitations: only left anterior descending artery is sampled with a very high success rate and coronary flow reserve cannot distinguish between micro vascular and macro vascular coronary disease. Therefore, it is very interesting to assess the additional diagnostic value over conventional wall motion analysis. Coronary flow reserve on left anterior descending artery is a strong and independent indicator of mortality, conferring additional prognostic value over wall motion analysis in patients with known or suspected coronary artery disease. A negative result on stress echocardiography with a normal coronary flow reserve confers an annual risk of death <1% in both patient groups, and allows effective risk stratification in other patients. A coronary flow reserve <2.0 is an additional parameter of ischaemia severity in the risk stratification of the stress echocardiographic response, whereas patients with a negative test for wall motion criteria and coronary flow reserve >2.0 during dipyridamole stress echocardiography have a favorable outcome.

Strain is a measure of deformation, in other words, lengthening or shortening. Strain and strain rate imaging allow the measurement of regional myocardial deformation to assess specific local and global function. Strain measures deformation whilst strain rate is the rate of change of the deformation. Both of these measures have been shown to provide complementary information about the clinical assessment of cardiac function [21]. Strain and strain rate can be estimated from echocardiographic images by several methods. In the simplest form strain can be derived from a parasternal short-axis M-Mode view, this however only gives estimates of anteroseptal and posterior wall thickening. To allow the assessment of other regions of the left ventricle, TDI techniques can be employed.

TDI, like all Doppler-derived measurements, is dependent upon the angle of insonation, so if the tissue under investigation is not moving perfectly in line with the ultrasound beam then the measurement obtained will be subject to inaccuracy. An other limit of TDI-derived-strain is the inability to quantify deformation in the radial plane. To be able to overcome these limitations

it has been developed a new technique known as 2D-strain. One important advantage over TDI techniques is that it is not limited by dependency on the angle of insonation. Several recent studies looking at ventricular function in specific groups of patients have reported practical ability to distinguish the abnormally from the normally contracting regions of ventricular walls. It provides new and complementary quantitative information about ventricular dyssynchrony and regional wall motion abnormalities [22]. Moreover recent studies have demonstrated the ability of 2D-SE to highlight the presence of CAD in patients where neither the coronary TC had given diagnostic results [23].

NUCLEAR CARDIOLOGY

Introduction

The nuclear imaging requires the intravenous distribution of radio-drug (isotopes or tracers). The two nuclear technique used in the clinical cardiology are the SPECT (Single Photon Emission Computed Tomography), also called myocardial scintigraphy and used more often, and the PET (Positron Emission Tomography). These techniques differ about the instrumentation, the acquisition, the resolution and the nucleds that are used. The main field of their use regards the evaluation of ischemic heart disease. In this case, they provide indication about the angiography and, if it is necessary, about the esecution of the PTCA (Percutaneous Transluminal Coronary Angioplasty). In particular, the indication to myocardial scintigraphy are substantially the same of the exercise test but it should be reserved for that case in which the execution of ergo metric test is difficult (such as: left brunch block, patient's inability) or in which the result of exercise test is uncertain. An additional, specific indication to myocardial scintigraphy is the research of the myocardial vitality [24]. Comparing with exercise test, myocardial scintigraphy can give information not only about the presence of inducible ischemia but also about its localization and quantification.

Evaluation of Myocardial Perfusion and Coronary Disease

Both techniques require the intravenous injection of radio-drugs at rest and stress, in order to produce images of mycardial uptake. The uptake is proportional to the regional blood flow. Normally, under stress the myocardial blood flow can enhance up five times compared to the rest condition; this for responding to the increased oxigen request. The most common SPECT perfusion tracers are Thallium-201 (^{201}Tl) and Technetium -99m ($^{99\text{m}}\text{Tc}$).

^{201}Tl is a potassium-mimetic tracers and enters in the myocardial cells using the Na/K-pump ATPase-dependent, so theoretically ^{201}Tl can accumulate in myocardial cell only if the cellular membrane is intact. $^{99\text{m}}\text{Tc}$ enters the myocytes with passive diffusion, directly proportionally to the regional coronary flow. The presence of a coronary stenosis results in a flow resistance with the development of a pressure gradient through stenosis and downward pressure drop in stenosis. However, the entity of the pressure gradient for a given degree of stenosis is variable in

direct relation to coronary flow. Basal coronary flow does not decrease significantly until stenosis reaches values of 80-85%. Coronary reserve flow begins to shrink by about 50% stenosis. Several factors (arterial pressure, heart rate, myocardial contractility) affect both baseline and hyperemic coronary flow. This translates in an irregular captation of the myocardial tracer.

The study of the coronary reserve is evaluated by letting the patient make physical effort (for example, by letting him/her cycling on a cyclette). Among the patients who are unable to exercise physically, is possible to enhance the blood flow through specific drugs. The most used drug is the dipyridamole, but can be used the adenosine and the dobutamine.

The images of SPECT and PET perfusion are commonly interpreted in a qualitative way that can be integrated through an automatic analysis quantitative. The images, indicating the normal myocardial perfusion, show a uniform uptake of the tracer in all the left ventricle (Figure 2). By contrast, the regions with a reduced blood flow, presents a reduction about the tracer uptake of variable degree, which can be study by a semi-quantitative scale (Figure 3). In addition, in order to map and reconstruct the hypoperfused areas, the left ventricle is “sliced” into three spatial axis (short axis, long horizontal long axis and vertical long axis (Figure 4).

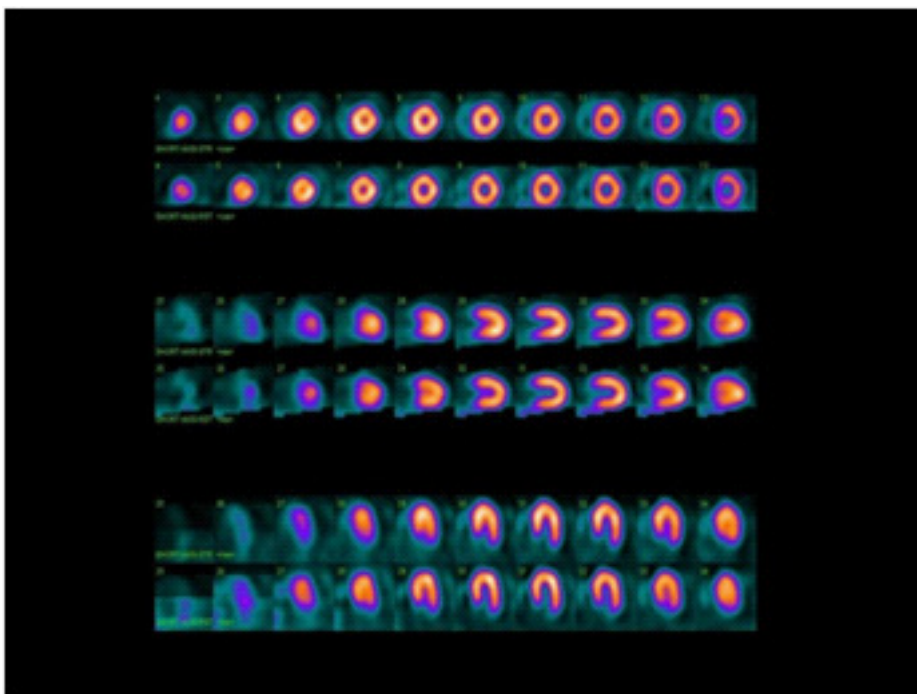


Figure 2: Uniform uptake of the tracer in all the left ventricle [25].

Leoncini M, Sciagrà R. Ruolo della scintigrafia miocardica di perfusione con tecnica gated SPECT nella valutazione diagnostica e prognostica dei pazienti con malattia coronarica cronica.

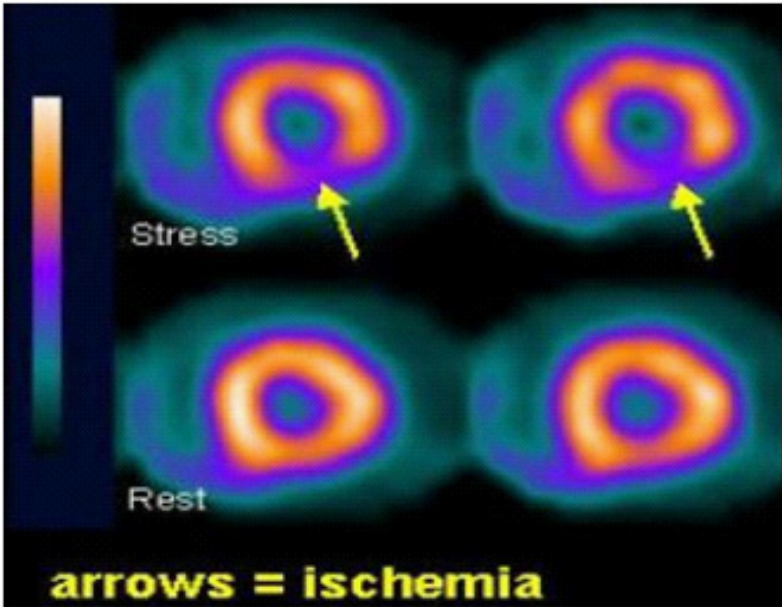


Figure 3: Reduction of the uptake tracer during stress. Ischemic pattern [25].

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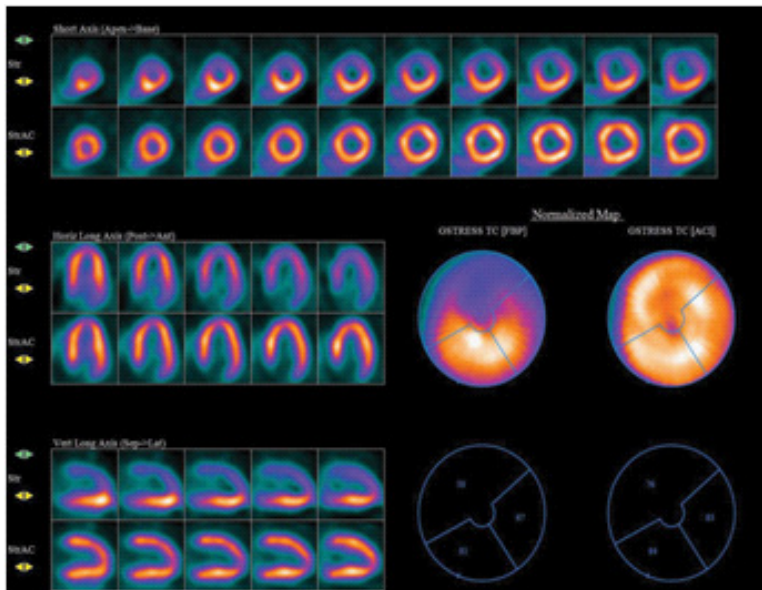


Figure 4: The left ventricle is sliced into three spatial axis [25].

Leoncini M, Sciagrà R. Ruolo della scintigrafia miocardica di perfusione con tecnica gated SPECT nella valutazione diagnostica e prognostica dei pazienti con malattia coronarica cronica.

A fourth reconstruction is called bull's eye, which is obtained by squashing the ventricle along the short axis. This last reconstruction is useful to get an overview of the entire organ (Figure 5). The reduced uptake of the tracer in a myocardial region that can be present both at rest and under stress, represents a permanent deficit, which is a myocardial infarction. The reduced uptake of the tracer only under stress with preserved uptake in the resting state, represents a reversible deficit, and It is indicative of myocardial ischaemic symptoms [25].

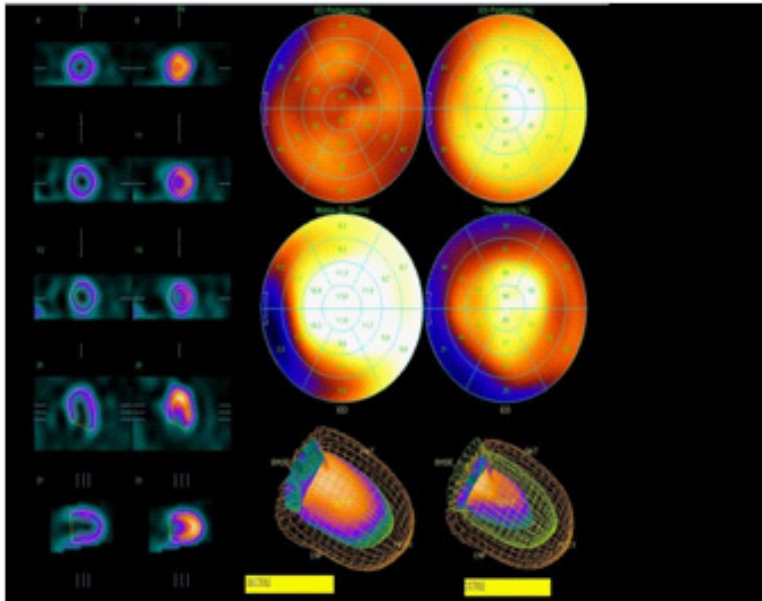


Figure 5: Bull's eye reconstruction and rendering 3D [25].

Leoncini M, Sciagrà R. Ruolo della scintigrafia miocardica di perfusione con tecnica gated SPECT nella valutazione diagnostica e prognostica dei pazienti con malattia coronarica cronica.

Research of the Myocardial Vitality

PET is considered the diagnostic test for the evaluation of the myocardial vitality. The tracer F.18 (FDG), evaluates the myocardial carbohydrate metabolism, and It is an index of myocardial vitality. The definition of “vital yocardial”, identifies a cardial region with function and reduced blood flow, but still metabolically active. The substrate used by the myocardium moves from the fatty acids and lactate to the glucose, leading an increase of the myocardial uptake of the FDG. In the definition mentioned above, from a pathophysiological point of view, It is possible recognize the stunned myocardium and the frozen myocardium. Stunned myocardium is reapedresented by the clinical model of acute myocardial infarction subjected to revascularization of the epicardial vessel. After acute occlusion, the effective treatment of the culprit lesion allows to restore coronary flow and preserve the vitality of myocardial tissue. In the early days contractility remains depressed with a gradual recovery; at this stage the evidence of myocardial vitality predicts contractile recovery and can therefore provide early prognostic information [26].

Frozen myocardium, is the consequence of a permanent reduction of secondary coronary flow to critical coronary stenosis; the clinical model is that of chronic ischemic cardiomyopathy [27]. The revascularization of dysfunctional but vital segments results in a significantly better survival than those of non-revascularized and also with a significant recovery of left ventricular function. The assumption of recovery of an acyetic or dysketic dysfunctional segment is the presence of a significant proportion of vital tissue in the subendocardial layer > 75%. Conversely, the presence of myocardial vitality in subepicardial layers can not result in functional recovery and contractile recovery, but it nevertheless has a benefit in terms of ventricular geometry and wall tension [28]. Nuclear cardiology allows the assessment of myocardial vitality, both with scintigraphy (**SPECT**) or positron chamber (**PET**) using radio isotopic tracers that allow for accurate and reliable myocardial and myocardial perfusion assessment. We can find three different situations:

- Deficiency of perfusion both under stress and rest: necrosis
- Effort perfusion defect with total recovery at rest: inducible ischemia
- Effortless perfusion defect with partial recovery at rest: necrosis + inducible ischemia

For the evaluation of myocardial vitality, PET uses metabolic tracers such as Fluoro-18 (**[F18] DG**) and myocardial perfusion tracers such as nitrogen-labeled ammonia (**[N3] H3**) for myocardial viability. Rubidio-82 or oxygen marked with oxygen-15 (**H2 [O15]**). The mismatch between hypoperfusion evidenced by ammonia and the persistent metabolic activity documented with FDG has proved to be accurate and reliable in the diagnosis of myocardial ischemia. The former is a consequence of a recent ischemic event, which is spontaneously settled or after therapy, where the contractile tissue remains temporarily underactive and with an altered metabolism, even though the flow has been restored. The latter (frozen myocardium) is characterized by an altered function, which is a consequence of a chronic hypoperfusion, probably created as a defensive mechanism against the ischaemia [24].

Evaluation of the Ventricular Function

In addition to the information about the perfusion and the metabolism, the SPECT and PET, when they are executed in a synchronous way to the ECG, and with a regular rhythm, they are able to provide information regarding: the systolic function (ejection fraction), the kinetics and the volume of the left ventricle. This technique is known as ECG-Gated acquisition. The integration between perfusion and functional parameters allows the sub division into three groups of patients with different risks of events (myocardial infarction and death):

- low-risk patients are the ones without inducible ischaemia and with FEVS post-stress > 30% or the patients with inducible moderate ischaemia, but with FEVS post-stress > 50%;
- intermediate risk patients are the ones with severe ischaemia and FEVS post-stress > 30% or the patients with moderate ischaemia and FEVS post-stress > 30% and ≤ 50 %;
- high-risk patients are the ones with FEVS post-stress < 30 % [29].

Multi slice Computed Tomography Angiography

Multi slice computed tomography angiography (**MSCT**) is increasingly used for noninvasive imaging of the coronary arteries in the diagnosis of coronary artery disease. Radiation exposure, however, is a potential limitation to a more extensive use of this imaging technique.

In patients with low or intermediate (15-50%) probability of CHD, MSCT is a viable alternative to conventional angiography. MSCT is mainly used for detecting or excluding significant stenosis in coronary arteries ($\geq 50\%$ diameter reduction).

Initially, clinical applications of MSCT were restricted to the detection of coronary calcium; at present time, its most important role is the visualization of the coronary artery lumen (noninvasive coronary angiography). In addition, it has become possible the assessment of non-stenotic coronary atherosclerotic plaques, coronary stents, or bypass grafts in selected situations [30].

MSCT has high sensitivity and excellent diagnostic accuracy [31]. Especially, the very high negative predictive value make MSCT a non-invasive imaging modality to exclude the presence of obstructive coronary lesions.

The most recent systems of MSCT is able to acquire over 256 slices simultaneously, allowing for visualization of anatomical details of coronary artery and its branches.

Comparing with invasive coronary angiography, the advantages of MSCT are to quantify and characterize atherosclerotic plaques, provide independent prognostic information for predicting cardiac events and mortality in patients with known or suspected CAD.

The entire procedure does not require more than 15 min, it start with the intravenous injection of contrast means. Imaging of the heart has always been technically challenging due to its continuous movement, so it is necessary an elective pre-medication, using beta-blocker to heart rate control (the image quality is affected by motion artifacts in patients with heart rates more than 65 bpm). Coronary artery has a diameter which ranges 3-5 mm in the main segments, and 1-1.5 mm in the distal segments. For adequate visualization of the coronary artery tree, with evidence of the coronary lumen and quantification of coronary stenosis with a minimal 20% change in the coronary diameter, the CT scanners need to provide a temporal resolution of between 200-250 ms and a spatial resolution of at least 0.5 mm. Later Technical developments such as 64- or more slice CT scanners allow for acquisition of large volume data in a very short time, further more MSCT system, as 256-slice or 320-slice system, has allowed for acquisition of whole-heart coverage in one gantry rotation with a slice thickness of 0.5 mm.

64-slice CT can achieve a maximum 4 cm longitudinal coverage in one heart beat, thus, 3-5 heart beats are normally required to cover the entire heart volume with, while with 256- and 320-slice CT can be achieved 12.8-cm and 16-cm of longitudinal coverag in a single heart beat,

with excellent image quality. Very high diagnostic accuracy has been reported with 320-slice CT angiography for detection of significant coronary stenosis in all coronary segments, regardless of size, cardiac rhythm or image quality. Furthermore, 320-slice CT enables visualization of coronary artery with sufficient image quality in patients with a trial fibrillation.

MSCT angiography is useful in diagnosis of coronary artery disease (**CAD**), especially in calcified plaques. Indeed, there is a direct correlation between coronary artery calcification and the extent and severity of atherosclerotic CAD. This relationships of coronary artery calcium with the amount of coronary plaque has increased interest in CT angiography for detection and quantification of coronary calcium in order to diagnose CAD.

The total coronary calcium is used as a way of predicting and stratifying the risk of CAD. Coronary artery calcium (**CAC**) scoring has showed that absence of calcium reliably rule out obstructive coronary artery stenoses, and that the amount of CAC is a strong predictor for risk assessment of myocardial infarction and sudden cardiac death, independent of conventional coronary risk factors. However, its predictive value is determined by the patients' symptoms.

In asymptomatic individuals, it has been reported that a zero CAC is associated with a very low (<1% per year) risk of major cardiac events, whereas in asymptomatic patients with extensive coronary calcification, the major cardiac events have been reported to be increased by up to 11-fold.

However, coronary stenosis are frequently found to be non-calcified, and highly calcified plaques are frequently non-obstructive. Thus, the value of a zero or low calcium score in symptomatic patients remains unclear. Studies have shown that zero or low calcium score is present in up to 8.7% of symptomatic patients with obstructive non-calcified plaques.

Frequently major adverse cardiac events are caused by plaque rupture, so it's important to characterize coronary atherosclerotic plaque: the calcium comprises only one component of plaque and non-calcified structures, such as a large necrotic core and thin fibrous cap are usually considered to indicate high inclination towards plaque rupture,

Coronary plaques can be characterized into the following three types based on the CT attenuation:

- *non-calcified plaques*: are defined as lesions with a radio density greater than neighbouring soft tissue but lower density than the contrast-enhanced coronary lumen;
- *calcified plaques* indicate lesions with density higher than contrast enhanced coronary artery lumen
- *mixed plaques* refer to lesions with non-calcified and calcified components (calcium component between 20-80%).

It is generally believed that lipid-rich plaques have a higher risk of rupture with consequent thrombosis than fibrotic plaques, thus, evaluation of different plaques based on measurements of CT attenuation has increased attention of physician.

Compared with intravascular ultrasound (**IVUS**), MSCT angiography revealed a overestimation on quantitative measurements of plaque areas and thickness. Furthermore, MSCT angiography can't detect unstable plaques, thus differentiation of lipid-rich content from fibrous content with MSCT remaining challenging due to overlap in the attenuation values of lipid and fibrous tissue.

Comparison with Coronary Artery

Despite rapid technical improvements and increased diagnostic accuracy achieved with latest MSCT scanners, invasive coronary angiography still remains the gold standard technique in the diagnosis of CAD. The spatial resolution of the latest MSCT scanners is 0.5 mm, which is quite close to the 0.2 mm that is available with invasive coronary angiography. Thus detection of coronary wall changes with current MSCT scanners can be achieved with high accuracy. However, the temporal resolution of 75 ms that is available with MSCT angiography is still inferior to the 20 ms with invasive coronary angiography, therefore, aggressive heart rate control is a necessity in most of the MSCT angiography examinations.

MSCT angiography should be used to identify those patients who would be most likely to benefit from invasive coronary angiography and reduce the number of invasive procedure in patients who do not have obstructive coronary disease.

Studies have shown that a reasonable number of patients with suspected CAD had normal coronary arteries or non-obstructive disease on invasive coronary angiography, suggesting that many unnecessary invasive angiography examinations were performed in the clinical evaluation of patients with suspected CAD.

It is generally agreed that CT is an imaging modality with high radiation on exposure; the effective radiation dose of a contrast-enhanced cardiac CT scan is 5-20 mSv. All possible precautions should be taken to keep the dose as low as possible, and considerations as to clinical indications for cardiac CT must always take radiation exposure into account [2].

CARDIAC MAGNETIC RESONANCE (CMR)

Cardiovascular magnetic resonance (**CMR**) imaging is a indispensable part of the diagnostic algorithm for evaluation in chronic ischemic disease and acute coronary syndrome (**ACS**). Magnetic resonance images are created using the relaxation behavior of hydrogen protons in a high magnetic field – typically 1.5T or 3.0T - following excitation by selective radiofrequency pulses. Main features are: high spatial and contrast image resolution, free choice of image plane and size of field of view allowing an excellent view on the heart and great vessels. Specific sequence modifications are needed to eliminate of image blurring due to motion incurred by the heart,

respiration and flowing blood. Cardiac motion and blood flow are frozen by synchronizing data acquisition to the electrical activity of the heart (electrocardiographic gating). Respiratory motion is stopped by performing the acquisition during breath-holds. Cardiac magnetic resonance (CMR) sequences are either spin-echo or gradient-echo based.

Spin-echo images offer a *morphologic view* on the heart and pericardium. In these sequences, the blood has a dark or black appearance, thus providing a natural contrast with the myocardium and vessel walls. Using a different weighting (e.g., T1- and T2-weighting), information can be achieved about tissue characteristics.

The **gradient-echo sequence** are used for *functional, perfusion, and angiographic imaging, and for cardiac tissue characterization*. For functional cardiac imaging, balanced steady-state free-precession (**SSFP**) imaging has become the gradient-echo sequence of choice. The high signal of blood at SSFP provides an excellent contrast with the myocardium. Images can be obtained with a high temporal resolution (e.g. every 30 ms) over the cardiac cycle and played in a cine loop, for to assess cardiac motion and deformation.

Paramagnetic gadolinium-based contrast agents are used in CMR and alter tissue magnetization and relaxation. Indeed, ultrafast gradient-echo imaging during the passage of intravenously administered gadolinium (**Gd**) through blood vessels and myocardium can be used for 3D-MR angiography, and evaluation of myocardial perfusion. The distribution volume of the Gd and differences in wash-in and wash-out kinetics can be utilized for cardiac tissue characterization (1). Cardiac magnetic resonance (**MR**) imaging is currently considered the gold standard for characterizing changes in myocardial structure, in particular to assess myocardial edema, necrosis, micro vascular injury, hemorrhage, focal fibrosis in ACS. The traditional MR sequences have significant limitations and provide only *qualitative* information. Recent developments in cardiac MR imaging techniques (T1, T2, mapping techniques), provide a *quantitative* data with regard to tissue characterization, myocardial perfusion and function [32]. *Myocardial edema* can be evaluated using *T2 mapping* techniques [33]. These have shown a superior performance compared to the traditional T2-weighted and STIR sequences, in acute ischemic injury. T1 mapping techniques performed both with and without contrast medium, enable to quantify diffuse myocardial fibrosis and to assess myocardial edema [32].

In ACS and, specifically, in acute MI patients, CMR is typically performed in the first two to five days after the acute event, and is very useful to detect the jeopardized myocardium - know as the myocardium without blood supply distally to the coronary artery occlusion - and that it could be necrotic if not timely reperfused. The jeopardized myocardium can be depicted by T2-weighted imaging, and appears bright ("hyper intense") compared to normal myocardium: this phenomenon helps to discriminate normal from ischemic myocardium. Similar information can be obtained by sequences such as pre-contrast T1 and T2 mapping. Myocardial perfusion - as sign of the adequacy of myocardial reperfusion - is studied using the first-pass of intravenously

injected Gd through the heart or by the early contrast enhanced (**ECE**) imaging, that detect the micro vascular obstruction. Areas of incomplete myocardial reperfusion are depicted as dark, non-enhancing areas. Moreover, in is chemically damaged myocardium, T1 and T2 relaxation times increase because of an increase of free water (caused by disturbances in cellular membrane function and presence of interstitial edema). The bright (“hyper intense”) in T2-weighted imaging persists at least one week after the acute event, so in patients with a clinical suspicion of ACS, detection of myocardial edema can be useful to identification of the infarct-related artery (**IRA**) whereas normal myocardial signal intensity on T2-weighted imaging excludes an a recent ischemic myocardial event. On the other hand, since myocardial edema may occur in other ‘acute’ cardiac disease, such as myocarditis or stress cardiomyopathy, the T2-weighted imaging should be integrated by cine imaging and late contrast enhanced (**LCE**). LCE imaging is performed 10-15 minutes post-gadolinium administration and is used to visualize the infarcted myocardium, yielding the most accurate assessment of the extent of myocardial necrosis, using a multi-slice two-dimensional or three-dimensional approach which surrounding the ventricles. As above named, the sequence is called LCE compared to ECE sequence performed immediately after gadolinium administration. LCE imaging is a well-validated tool for infarct sizing independent of the time post-infarction.

The contrast kinetics and the distribution volume of gadolinium are damaged in the infarcted myocardium, and so there is an increased accumulation of gadolinium molecules in extracellular compartment and consequently *greater shortening of T1-relaxation time* in the irreversibly damaged myocardium compared to normal myocardium. The use of an inversion-recovery pre-pulse with an appropriate inversion time enables to nullify the signal of normal myocardium which results in an excellent detection of infarcted myocardium, expressed as a volume or as percentage of LV mass. CMR allows to detect a small infarct volumes (even less than 1g of myocardial tissue).

A myocardial infarct is typically located in one of the coronary perfusion territories, is always subendocardial located and has a variable trans mural extent

A key characteristic of myocardial tissue is its low regenerative capacity because myocytes are terminally differentiated, having lost the capacity to renew damaged myocardium. Consequently, irreversibly damaged myocardium is replaced by an a functional fibrotic scar, a process deemed to take several weeks. Thus, the amount of contractile tissue lost - or the infarct size - reflects infarct severity, is a crucial determinant of adverse LV remodeling.

CMR is useful to show the intra myocardial hemorrhage (**IMH**) in the infarct core, provoke fu reperfusion of ischemic myocardium with irreversible micro vascular damage, with massive red blood extravasation into the extracellular space. IMH is associated with longer ischemia times, severity of flow depression before reperfusion and extent of necrosis.

Taking advantage of the paramagnetic properties of the hemoglobin breakdown product

-deoxyhemoglobin - causing shortening of T2-relaxation times, T2-weighted CMR can be used to noninvasively demonstrate IMH, hemorrhagic infarct presents with a central dark appearance.

Moreover, CMR is useful to stratify the increased risk for arrhythmias and sudden cardiac death in patients with a recent history of MI. Whereas the center of the infarcted myocardium evolves towards a dense fibrous scar incapable of depolarization, the infarct border zone in contrast - containing a mixture of non-viable and viable myocardium - may be an arrhythmogenic substrate potentially causing ventricular arrhythmias and sudden cardiac death. CMR detect infarct tissue heterogeneity: dense fibrotic myocardium at LCE imaging has typically a high signal intensity (**SI**). Lower SI, the so-called 'gray' myocardium, corresponds to infarct areas with variable amounts of fibrosis and myocytes. The current value of CMR, at present, in ACS patients is primarily in the diagnostic work-up of patients with acute chest pain showing normal or non-obstructed coronaries at cardiac catheterization. The diagnostic problem to solve is whether these patients have a spontaneous recanalization of the culprit lesion, obstruction of one of the smaller side branches, another cardiac disease causing ECG changes and release of cardiac enzymes, or an extra cardiac origin of their complaints. In case of spontaneous clot resolution, CMR is often able to detect signs of myocardial ischemic damage, such as myocardial edema, LCE and functional impairment in a coronary artery perfusion territory. Moreover, CMR allows to detect infarct-related complications imaging such as aneurysm, valve leakage, post-infarction pericardial injury and to differentiating true from false aneurysms. Using a comprehensive CMR approach even rare complications, such as a dissecting myocardial hematoma, can reliably be detected. CMR is definitely the best imaging modality to detect ventricular thrombi. In particular contrast-enhanced imaging allows to depict or to exclude even small thrombi, typically appearing as dark structures surrounded by the contrast-enhanced blood [32].

Stress Test Cardiac RMN

A stress test is indicated in symptomatic patients with typical or atypical chest pain or correlates suspected of being due to CAD and who have a low or intermediate cardiovascular risk profile, as well as in asymptomatic patients with high cardiovascular risk profiles, such as diabetics. Exercise electrocardiography (**ECG**) is usually the first-level stress test, but this may not be appropriate for some patients (e.g., those with limited physical capacity) or non diagnostic (e.g., due to not reaching the target heart rate). Therefore, stress tests, noninvasive imaging, are frequently used, as cardiac magnetic resonance (**CMR**). Furthermore, myocardial perfusion analysis during stress is possible with CMR. Stress perfusion CMR imaging alone, or in combination with rest perfusion CMR imaging is an accurate technique to detecting hemodynamically significant stenosis. Intravenous administration of vasodilator (e.g. adenosine, dipyridamole) causes a preferential flow towards normally perfused myocardium at the expense of blood flow to areas perfused by hemodynamically significant stenoses. *Hypo-perfused myocardium* appears as *dark, non-enhancing myocardium* at first-pass myocardial perfusion CMR. Combining rest-stress perfusion allows calculation of myocardial perfusion reserve [32].

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