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Mexican Consensus of Chronic Ischemic Heart Disease. Non-invasive diagnosis, classification, and stratification. Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE)

Consenso Mexicano sobre la Cardiopatía Isquémica Crónica. Diagnóstico, clasificación y estratificación no invasivos. Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular (COMECITE)

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ABSTRACT

The current approach for the diagnosis of coronary syndromes includes diverse plans, according to the attending physicians' individual preferences, as well as the institutional protocols mostly based on classical strategies and concepts. This paper summarizes a multidisciplinary consensus group that included thorough research of publications containing the evidence-based strategies for the more objective approach to discriminate the coronary cause. The statement recommendations stress the relevance of anamnesis and physical examination, the gender differences, the usefulness of the non-invasive tests, and the benefits of decisions based on a multidisciplinary approach.

RESUMEN

El abordaje para el diagnóstico de los síndromes coronarios incluye diversos métodos de acuerdo con las preferencias individuales de cada médico tratante así como con los protocolos institucionales basados, en su mayoría, en estrategias y conceptos clásicos. Este artículo es resultado del trabajo de un grupo de consenso multidisciplinario tras una investigación exhaustiva de las publicaciones que contienen las estrategias basadas en la evidencia científica para una estrategia más eficiente con el fin de descartar la causa coronaria. Las recomendaciones del consenso consideran la relevancia de la anamnesis y el examen físico, las diferencias de género, la utilidad de las pruebas no invasivas y los beneficios de las decisiones de grupos de trabajo.

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INTRODUCTION

The current status of the diagnosis, stratification, and selection of patients with chronic ischemic heart disease implies diverse strategies, some without a document that puts the absolute value on them. Many patients are under the care of a single physician, who makes each diagnostic step's decisions, and others under multidisciplinary groups with precisely designed protocols.

This document represents the consensus and point of view of a group of experts in Ischemic Heart Disease in Mexico, organized by the Mexican College of Interventional Cardiology and Endovascular Therapy. The College invited the most representative societies, associations, and colleges of cardiology in our country to study, discuss and agree on the non-invasive diagnostic approach, stratification, and selection of patients with chronic ischemic heart disease.

Ischemic heart disease has a prevalence of around 30% in adults over 40 years old in Mexico, being the leading cause of death. The diagnostic approach, stratification, and selection of patients for cardiac catheterization vary depending on whether the practice is institutional or private and the technological resources, regardless of what is stipulated by the American College of Cardiology and American Heart Association guidelines.

The group of experts that make up this consensus after an extensive review of the literature, discussion, and even surveys presents the following statements in the analysis and study of Chronic Ischemic Heart Disease and its diagnostic approach and patient selection for Percutaneous Coronary Interventional Therapy.

The United States of North America and European guidelines are hardly applicable in the Mexican population due to different health policies, medical expenses, diet, physical habits, and different behavior. The spectrum of coronary disease discrimination methods ranges from very low sensitivity old tests, towards sophisticated imaging tests, to multimodal imaging protocols.

This situation justifies the elaboration of a Mexican statement of clinical consensus to determine which are the minimum acceptable criteria to define which patients should be treated by revascularization or not. The consensus will seek to propose strategies with the highest diagnostic precision and the least possible error to avoid, as much as possible, uncertain diagnosis.

The main conditions to evaluate will be:

1. Group versus isolated physician strategies.
2. Functional versus anatomical diagnosis.
3. Diagnosis based solely on the electrocardiogram versus image.
4. Consider whether the EKG stress test and coronary calcium contains enough coronary discrimination accuracy, and
5. Direct cardiac catheterization in patients with symptoms suggestive of myocardial ischemia and high possibility of atherosclerosis.

METHODOLOGY

The consensus group conformed from COMECITE members, elected chair, and co-chair, followed by the rest's specific functions and invitation for other medical associations to participate.

The meetings took a nominal group technique format, which consists of the face-to-face discussion on video conference, in which each member presents their proposal and their reasons, without a time limit. Delphi rounds finally solved disagreements.[1-4]

AUTHORSHIP

The consensus group will define the authors' nomination from the beginning of the consensus work and modify it during its process. According to the International Committee of Medical Journal Editors (ICMJE),[5] all the people who contribute and who strictly comply with every one of the following aspects will be authors:

1. Contribute substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data.
2. Write the work or critically review it.
3. Approve the final version to be published.
4. Confirm the accuracy and completeness concerning every part of the work.

The acknowledgments section will mention the contributors who have not complied with every one of the four points outlined above. This section will include all participants who have contributed to the consensus, whether in decision-making, literature review, open discussion, and anonymous voting.[5]

The magnitude of consensus' contribution ordered the authorship and the corresponding author designation, with a preponderance of the person who originated the idea and who presides and coordinates. In case of disagreement and dispute over the order, an anonymous vote in a ranking format of importance decides, and, in extreme cases, the consensus may call an internal or external judge.

CLINICAL ASPECTS

The clinical picture of coronary heart disease varies in presentation forms since ancient descriptions. William Heberden, in 1768, published his observations about angina pectoris and sudden death, detailing the chest pain in different locations and irradiations, sometimes with paresthesia in the hands; it may appear during the march, mainly uphill; the movement of a horse or carriage or even swallowing, coughing, defecating or any mental disorder may trigger it.

That classic description included some cases of paroxysmal nocturnal dyspnea, possible arrhythmia and sudden death, possible recovery with long term physical activity, and response to opium.[6]

The art of diagnosis is a matter of daily medical practice; the interpretation of the clinical manifestations related to coronary heart disease is not an exception; unfortunately, many patients seek attention under atypical symptoms. This chapter will review every significant clinical aspect in the characterization of coronary syndromes. It is crucial to say that misdiagnosis may lead to complications with lethal potential and overdiagnosis to increased costs over the health systems.

Chest pain is the chief complaint that brings the patient to medical care and triggers the protocol to discriminate against coronary heart disease. We can consider two conditions, either typical or atypical pain, both either chronic or in acute presentation; being the chronic the one that lasts more than 30-60 days and it is stable if it preserves unchanged pattern concerning the intensity, duration, frequency, tolerance to physical activity, time to relief after exercise and dose of vasodilator to stop the pain. Worsening on any or some of these aspects leads to progressive angina.

The Canadian Cardiovascular Society classified chronic angina into four clinical stages, on the following classes:[7]

1. Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous, rapid, or prolonged exertion at work or recreation
2. Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in the cold, or under emotional stress, only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs, at an average pace and in normal conditions.
3. Limitation of ordinary physical activity.
4. Inability to carry on any physical activity without discomfort, the anginal syndrome may happen at rest.

Unstable angina is a syndrome with significant variation in presentation but may classify as follows: progressive, new-onset, prolonged and recurrent, variant angina, post-myocardial, and post revascularization angina.[8]

In 1989 Eugene Braunwald published his unstable angina classification, recognizing the onset as less than two months, but giving the worst prognosis for the more recent start, presentation at rest, non-related to extracardiac conditions, and soon after an acute myocardial infarction.[9]

It is important to note that chest pain's characterization is not reliable to rule out the coronary origin. In contrast, typical pain on a high-risk profile and abnormal electrocardiogram may raise almost the certainty of being myocardial ischemia, the atypical pain on a low-risk scenario, and normal electrocardiogram never completely discriminates the possible cardiovascular

outcome. Indeed, these are the cases with enhanced risk of inappropriate early discharge and further complications, including legal ones.

For this reason, many investigators released several scores to grade the possibility of lousy prognosis related to acute coronary processes; the more frequent ones include the TIMI score, HEART score, Vancouver Chest Pain Rule,[10] and North American Chest Pain Rule. These scores enhance their sensitivity with the help of the electrocardiogram and the measurement of cardiac markers; their problem is the lack of absolute reliability; the TIMI 0 score has an unacceptably high 1.8% 30-day incidence cardiac events.[11]

David Markel et al describe several frequent arguments for discharge based on only clinical and bedside tests, considering young and healthy people, atypical symptoms, palpation reproducible pain, normal electrocardiogram, normal single troponin after six hours of initial symptoms, negative serial troponins and electrocardiograms, cero TIMI score and previous negative stress test. Note that every statement may lead to inappropriate early discharge from the Emergency Department.[12]

The clinical picture may qualify as typical or atypical, being the first something similar to Heberden's description. Often, a quick priory interrogatory may lead to an atypical presentation that later becomes typical after a more detailed and dedicated conversation, sometimes with the expert or a person more inclined to diagnose better. Note that the narrative of the symptoms varies with cultural differences.

The pain felt as pressure or aching has a weak predictive value with a likelihood of one to two,[13] whereas stabbing and sharp nature gives a high possibility of non-coronary pain.[14] The pain in a specific area of the chest does not help either for positive or negative prediction, neither to establish the infarction localization, except for abdominal pain and digestive symptoms that are more prone for inferior myocardial infarction;[15] the abdominal pain may herald acute myocardial infarction in 10% of cases.[16] In patients with previous angina or myocardial infarction, it helps qualify the pain's similarity with the experience before.[17]

The localization in the right upper chest square is more predictive than the left lower one; women lead more radiation to the neck and back than men.[18] The radiation of the pain is always part of every interrogation, but only radiation to shoulders or both arms shows a 4.07 adjusted positive likelihood ratio for acute myocardial infarction.[19] The severity of the pain is not able to differentiate the coronary origin.[20] The pain's duration has many classical descriptions, which gives less likelihood to the extremes of hours or days and few seconds lasting episodes, without confirmatory evidence yet, although the maximal pain at onset may lead to suspect of aortic dissection.

Several maneuvers may help the diagnosis: the pain triggered by every deep inspiration may lead towards a pleuritic one (sometimes found in pulmonary embolism), but it lacks utility if present in some inspirations and absent in others. The pain at the neck or shoulders' movement or positive to pressure may lead to a musculoskeletal problem, and the partial or total relief at leaning forward may resemble pericarditis.[18] The accompanying symptoms, such as nausea, vomiting, and diaphoresis, have conflicting information from several publications.[19]

The relationship with exercise may direct more to a coronary problem, both for angina and myocardial infarction. The relationship with emotions does not have clear evidence for prediction but classically is related to coronary problems, although it gives rise to suspicion for stress-induced cardiomyopathy.[21,22] The relief after sublingual nitroglycerine does not have predictive value, as classically considered; this drug can relax blood vessels and esophagus.[23] The same happens for the response to cocktails for gastrointestinal conditions is neither.[24] After several minutes at rest, the relief of pain, although useful for chronic stable angina, is not for help to rule out the acute coronary problem.[25]

Fatih Aydin et al., from Turkey, in 2019, developed a score based only on the chest pain, without other aspects, on 484 patients on screening for chest pain. They compared the score against the stress test and completed the cases with nuclear scan and cardiac catheterization; finally, they found a significant power to suspect or rule out acute coronary syndrome.[26] They gave one to two points for seven questions

relating to several aspects of pain, such as type, duration, localization, accompanying symptoms, and triggering factors, adding one more point if the patient is diabetic or older than 75 years. Of course, it is a reasonable effort but needs more time and reproducibility.

Angina equivalent often heralds myocardial ischemia and infarction; this refers to the patients seeking medical attention for an event where the chest pain is not the cardinal manifestation but other symptoms. The most common are dyspnea, isolated pain in the arm, neck, jaw, or shoulder, diaphoresis, syncope, nausea and vomiting, anxiety, delirium, and palpitations.[27]

Gokhroo et al published, in 2016, a study based on only clinical aspects to determine predictors for acute myocardial infarction on 10,867. The study showed that typical chest pain (OR: 2.72, $p < 0.0001$) and diaphoresis (OR: 97.06, $p < 0.0001$) predicted ST-elevation myocardial infarction (STEMI), so based on this observation, diaphoresis should be considered the more powerful predictor of STEMI. Arm, back and epigastric pain, dyspnea, nausea, vomiting, and vertigo favored STEMI over non-ST elevation acute coronary syndrome (NSTE-ACS); palpitations, xerostomia, atypical chest pain, and throat pain favored NSTE-ACS over STEMI.[28]

The same year, Morten et al. performed a study on ambulances by the Danish Tele-database's telemedical registry on 17,398 patients. They found that, although dyspnea alone is less predictive for myocardial infarction, it associates with more than four-times lethality than chest pain (21 versus 5%) at 30 days, when both symptoms are related to a myocardial infarction; the 30-day lethality of cardiac arrest was 38%. The respective numbers at four years were 60, 23, and 51%.[28]

Vulnerable groups include young people who are frequently discharged without more tests because of age, although growing risk factors are associated with acute coronary syndromes in youth either related to atherosclerosis or recreational drugs. Symptoms of myocardial ischemia must lead to a dedicated protocol to rule out the coronary source in this group.[29]

Syncope may happen as a single symptom related to acute coronary syndrome. Myocardial ischemia is unlikely to cause the transitory circulatory collapse by itself but indirectly through arrhythmias, such as complex ventricular one, atrioventricular blockage, or the combination of bradycardia and hypotension during inferior wall myocardial infarction. Otherwise, syncope may consist of a prodrome towards sudden cardiac death.[30,31]

The elderly represents variable difficulties on the diagnosis; they share the same features for typical and atypical presentation but with the undesirable transient global disorder of cognition. Up to 28% of these patients complicate delirium after an acute myocardial infarction, but delirium may be the initial and single complaint during the acute myocardial ischemia.[32]

Women are unique and complex patients because of their lack of efficient survey for coronary heart disease. There are several reasons for this problem, starting with the generalized concept that heart attack is a «men's disease» and followed the concept that women have different forms for clinical presentation, including more atypical chest pain, as well as non-chest pain; but of course, there is a gender continuum where there are many features shared with men. The current difference in the outcome against men may be related to less diagnosis and more delay for hospital admission and treatment.[33]

To further complicate the diagnosis, there is a substantial number of silent cases, with a significant danger due to the lack of awareness that makes them seek less for cardiac attention. It is widespread in people with diabetes due to cardiac autonomic dysfunction.[34]

The dedicated anamnesis of the chest pain may increase or reduce the suspicion for a coronary problem but never rules it out.

Family history

The detailed family history for any coronary heart disease and sudden death is indispensable in every clinical chart, with particular consideration regarding parents and siblings but trying to detect at least three generations. The questionnaire must be precise about the medical condition after the information of «heart attack» because sometimes this comes as a light common expression; often, such

precedent corresponds to sudden death. The patient may first say that the relative died from a heart attack, but after a detailed interrogation, the death happened suddenly; it is so frequent to interpret sudden death as a «heart attack», even by physicians. The typical case corresponds to the question:

1. What did your relative die of?
2. He died of a heart attack
3. Can you describe in detail the conditions of death?
4. He fell asleep and did not wake up or suddenly became unconscious and we were unable to revive him, etc.

A family history of sudden death is more frequent among survivors of myocardial infarction with ventricular fibrillation than controls without (OR 2.27, 95% CI, 1.84-4.03).[35] There is also more myocardial infarction related sudden cardiac death, with this first-degree family history than otherwise (OR, 1.6, CI 95%, 1.2-2.2, $p < 0.01$).[36,37]

There is major prevalence of confirmed coronary disease by computed tomographic angiography on subjects with positive family history than the controls (40 vs 30%, $p < 0.001$), more obstructive lesions (11 vs 7%, $p < 0.001$), more annual rate of myocardial infarction (0.5 vs 0.2%, log-rank $p = 0.001$) and strongest positive predict for myocardial infarction (hazard ratio 2.6, 95% confidence interval 1.4 to 4.8, $p = 0.002$).[38] The positive family history results more predictive for female patients before 65 years old (76 vs 62%, $p = 0.0026$), with more transmission of risk over sisters than over brothers.[39]

The coronary events are less in persons with both parents living 80 years or more (relative odds 0.49, 95% CI: 0.31-0.77) against people without longevity history (relative odds of 1.93, 95% CI: 1.25-3.00). The Framingham heart study found the parental transmission indeed as an independent predictor for myocardial infarction even after correction for other variables, considering predictive a father's event under 55 and mother's under 65 years old, but the risk from sibling's history is even higher (1.99; 95% CI, 1.32-3.00 versus 1.45; 95% CI, 1.02-2.05).[40,41]

The family transmission of coronary and brain vascular risk is significant even in persons with zero coronary artery calcium scores.[42] Hosseini et al. found younger age on a first acute coronary event on positive family history (59 ± 11 versus 64 ± , $p < 0.001$); they also had more smoking and hypertension; besides they had more frequent left-main coronary disease (5.5 versus 3.2%, $p = 0.017$) and more unstable coronary syndrome.[43,44]

The odd rate of myocardial infarction is 1.67 for positive history in one parent, 2.36 for one parent less than 50 years old, 2.9 for two parents, and 6.56 for both parents infarcted before 50 years old.[45] The risk of lethal coronary disease is 3.8 to 15 times if an identical twin died before 75 years old; it is three times higher on identical than non-identical twins, and the risk increases the earlier the other twin died. There is evidence of early carotid and aortic stiffness in children from hypertensive parents.[46]

The current evidence of family penetration for cardiovascular disease justifies the systematic screening and multidisciplinary intervention to prevent such events in relatives without cardiovascular events. This strategy may save many lives.

Personal history

The personal history must include former cardiovascular disease and other chronic problems but especially the known coronary risk factors, yet their presence may increase the possibility for a coronary source.

Let us start with the female gender because of the proclivity to underdiagnose myocardial ischemia in women. The official 2018 Mexican statistics inform that the primary cause of death is heart disease, either in men and women, being diabetes mellitus the second cause in both, but cerebrovascular disease the fourth cause in women and the seventh in men. The same year, the sum of heart disease, diabetes mellitus, and stroke constituted 138,434 deaths only in women, 44% of the total female deaths that year, and 3.2 times the total of malignant tumors.[47]

Since the Framingham study, the increase of cardiovascular disease in women is not a

rapid curve but a tendency towards the next years, with a delay of ten years after male cardiovascular events. The lack of estrogens is related to physiologic changes in the circulation, particularly more tendency to vasoconstriction and lower levels of plasminogen activator inhibitor. There is controversy regarding the association with metabolic changes, but women share the other coronary risk factors with men, possibly with the worst outcome concerning low HDL-cholesterol, diabetes, and hypertriglyceridemia.[48]

Although menopause points to the start of the female cardiovascular decline, there is evidence that symptoms of menopause, such as hot flushes and nocturnal diaphoresis, possess the most potent hazard ratio compared with asymptomatic menopause (1.344, 95% confidence interval [CI] = 1.262-1.43, $p < 0.001$).[49] The menopause risk is mostly related to higher testosterone levels, especially after bilateral oophorectomy.[50] Endometriosis imposes elevated combined risk for coronary heart disease (combined: myocardial infarction, confirmed angina by angiography, and any coronary revascularization) (relative risk 1.62; 1.39-1.89); the younger patients have a higher risk (≤ 40 years: 3.08; 2.02-4.70). This elevated risk possibly follows chronic systemic inflammation, enhanced oxidative stress, and abnormal lipid profile.[51]

Is gender a cardiovascular risk factor? It is important to analyze the connotation of the male gender as a major risk factor for ischemic heart disease, discriminating women, with the consequent apathy in their study of cardiovascular disease, resulting in an error since this stigmatization has generated a higher incidence of underdiagnosis and therefore higher morbidity and mortality.[52,53]

Today the women in red (Mexican Cardiologists) are on an exceptional crusade seeking complete care for women in the area of cardiovascular disease.

There is another marginalized group, the transgender community. These people also occupy a preponderant place in suffering cardiovascular complications, particularly due to their hormone therapy.

Therefore, we must fight for health equality regardless of gender.

In the original article «Cardiovascular Disease Risk Factors and Myocardial infarction in Transgender Population»,[54,55] the authors conclude that the transgender population had more history of myocardial infarction than the cisgender population, except in transgender women compared to cisgender men.

Age is a classical independent coronary risk factor, although the risk does not increase continuously with aging. Although independent risk, it is strongly associated with other modifiable risk factors and family history.[56] Every clinical history must include the classical coronary risk factors mostly for primary and secondary prevention more than for diagnosis; of course, the more risk factors predict more possibilities for a current coronary syndrome, but this approach renders a modest prognostic accuracy.[53] The predictive potency of classic coronary risk factors during an acute coronary event is not significant in women; in men, only diabetes and family history are predictive with 2.4 and 2.1 relative risks.[57]

The clinical history must always record any precedent or sign of peripheral arterial disease, in any of its manifestations: claudication, amputation for arterial vascular insufficiency, vascular reconstruction, bypass surgery, percutaneous intervention in the extremities, documented aortic aneurysm, lack of pulses, or a brachial ankle index of < 0.8 in any of the legs, as this is related to the increased relative risk for major cardiovascular (2.07; 95% confidence interval [CI]: 1.41-3.06; $p < 0.001$) events such as stroke (3.22; 95% CI: 1.80-5.75; $p < 0.001$), myocardial infarction (2.15; 95% CI: 1.29-3.59; $p = 0.003$), all-cause mortality (2.21; 95% CI: 1.33-3.69; $p = 0.002$), and readmissions for cardiac reasons (1.83; 95% CI: 1.24-2.70; $p = 0.003$).[58]

Erectile dysfunction is related, not only to the possibility for coronary disease but may predict its seriousness. Patients with lower scores of the international index of erectile dysfunction have significantly more involvement of the left main (4.3 versus 18.4%, $p = 0.035$), three vessel disease (17 versus 39.5%, $p = 0.021$) and combined left main + three vessel disease (21.3 versus 55.3%, $p = 0.0012$).[59]

Finally, patients with a history of coronary heart disease are at a permanent high risk for

recurrent events, especially if inefficient risk factors modification. These patients may help a lot with differentiating the symptoms from the non-cardiac origin.

The following diagnostic tools are based on the pre-test probability for coronary artery disease. The current work will not include the such pre-test process, but the reader may utilize a calculator on line.[60]

STRESS ELECTROCARDIOGRAM

The stress electrocardiogram test is the most common non-invasive diagnostic method to evaluate ischemic heart disease. However, there are many aspects to consider. In some meta-analyses, it is good at ruling out rather than confirming; it detects ischemia but not the presence of atherosclerosis in the absence of coronary flow limitations. Despite this, its wide distribution, feasibility, and cost keep it useful if carried out correctly. The pretest probability (the patient's probability of coronary artery disease) is indispensable for coronary artery disease suspicion, considering the clinical characteristics, such as age, sex, time of pain, and personal and family history.[61,62]

The estimation of pretest probability reduces false negatives and positives. The patients able to exercise, without abnormal resting electrocardiogram and no revascularization history, may perform this test. The «non-diagnostic» or nonspecific test renders higher mortality than the positive since the search for ischemia is frequently not continued, being the goal to identify high-risk patients such as those with multiple vessel disease.[63]

Unfortunately, the stress electrocardiogram possesses low sensibility to discriminate coronary heart disease, with the unfortunate suboptimal ruling out potency; that is why the current European guidelines indicates this option, only as alternative when the image modalities are not available.[64]

The standard criterion for abnormal response is ST-segment depression straight or descending, 1 mm for 80 ms, after the J point, or 1 mm elevation of the ST segment, on at least two contiguous leads. The sensitivity is 68% and specificity 77%; these values decrease even more in women who tend to have higher false positives, enhancing the need for an adequate pretest evaluation. The test contraindications include ventricular hypertrophy, left bundle branch block, beta-blockade, digoxin, preexcitation, and any alteration of the ST segment at rest. The ST at least 1.5 mm depression into the first two stages, identifies patients with higher risk and mortality.[65-71]

Other aspects, besides the ST segment changes, predict coronary heart disease and are low exercise capacity, chronotropic incompetence (inability to reach 85% of the frequency heart rate), inadequate recovery of post-exertional heart rate (less than 12x' reduction in the first minute or less than 22 up to the second). The abnormal response of blood pressure to exercise (the drop in systolic pressure may reflect multivessel disease.[72-79]

The Duke Treadmill Score classifies into risk groups: low-risk score predicts 60% off-significant disease, and high-risk predicts 74% multivessel or left main coronary disease. The Low-risk annual mortality is 0.25%, and the high-risk is 5%. The use of the Duke score also correlates with the severity of coronary disease.[80-85]

STRESS ECHOCARDIOGRAPHY

Stress echocardiography is currently a recognized method that intervenes in clinical decision-making in patients with known or suspected coronary artery disease, with proven diagnostic precision and prognostic value.

The incorporation of two-dimensional echocardiography substantially improved the recognition of exercise-induced regional myocardial ischemia in areas supplied by stenotic coronary arteries. Several advances allow greater diagnostic accuracy, including second harmonic, tissue Doppler, contrast infusion, and echo-enhancers that allow opacification to delineate the endocardial borders interface in both ventricles.

The current software enables rapid digitization and display of images in various formats and synchronizes them at different test stages to increase the diagnostic accuracy.

Compared to other forms of stress imaging, echocardiography has several significant

advantages, being very versatile, allowing from the resting images at the beginning, rapid recognition of many disorders that can contribute to the development of cardiac symptoms, such as valvular heart disease, hypertrophic cardiomyopathy, aortic dissection, diastolic dysfunction, arterial hypertension, and pericardial effusion. Other baseline information, such as left ventricular hypertrophy in hypertensive patients, can influence prognosis and therapeutic decision-making, as well as the contraindication to proceed in the case of aortic dissection, tamponade, or severe valve disease.

Throughout the study, the patient can be monitored, specifying the onset of myocardial ischemia, which can guide the type and urgency of treatment required.[86]

The stress echocardiogram is a first-line strategy in diagnosing and following-up ischemic heart disease as a suspected or established diagnosis, under the following indications:[87]

1. Diagnosis of chest pain suspected of angina in patients with an intermediate probability of coronary artery disease. The European guidelines indicate that the imaging stress test is the preferred modality for all patients with a pretest probability of 15-85% in expert hands.
2. Assessment of the functional significance of intermediate severity after coronary angiography.
3. Diagnosis of chest pain in patients with known coronary artery disease (including previous percutaneous coronary intervention and surgical coronary revascularization) who present angina symptoms.
4. Evaluation of cardiac etiology of dyspnea; the prevalence rate of angina increases with increasing dyspnea severity. Approximately one-third of patients referred to a stress test for dyspnea will render positive for ischemia. The positive test predictors include male gender, coronary history, and abnormal wall motion on resting echocardiogram.
5. Prognostic assessment and risk stratification after myocardial infarction.
6. Risk stratification before intermediate and high-risk non-cardiac surgery in patients with chronic angina or previous myocardial infarction.

The exercise stress echocardiography is the test of choice if the patient can exercise for most myocardial ischemia evaluation because it preserves normal electromechanical response and can provide important prognostic information on functional status. To acquire reliable sensitivity, the patient must reach 80% of the predicted workload.

The exercise echocardiogram can estimate the myocardial viability by making careful observation of the segmental wall motion. The accuracy in detecting hibernating myocardium is similar to positron emission tomography (PET).

The hemodynamic response to exercise can discriminate ischemic symptoms from other causes. It is almost always possible to control the most complications, such as hypertension or arrhythmias.

When the patient cannot exercise, the pharmacological stress echocardiography is the choice, with dobutamine more frequently. Other catecholamines, such as epinephrine, isoproterenol, and arbutamine, have limited indications due to side effects. In the presence of dobutamine infusion, ischemia occurs depending on the degree of obstruction.[88-90]

The possible ventricular response during the dobutamine infusion includes contractile improvement (normal), worsening of contractility (ischemia), improvement in contractility and therefore functional (viability), ischemia-viability: biphasic response with contractile improvement at low doses of dobutamine and worsening at high doses (ischemia-viability) and akinesis or dyskinesis with no improvement in regional function (fibrosis or scar).

In addition to the search for myocardial ischemia, dobutamine stress echocardiography is the most used modality to assess myocardial viability at low dobutamine dose (from 2.5 to 20 mg/kg/min). Sustained ventricular tachycardia during dobutamine infusion may strongly indicate ischemia.

Dipyridamole provokes hyperemia and ischemia; the hyperemic effect works for myocardial perfusion test with radionuclides and magnetic resonance; the ischemic effect works for functional echocardiography and magnetic resonance.

The precision of the dipyridamole echocardiogram implies 72% and 95% sensitivity and specificity. The rapid high-dose or atropine-boosted protocol test's sensitivity and specificity are identical to those obtained by dobutamine stress echocardiography.

The strain and strain rate assess the longitudinally oriented fibers through the apical window; these fibers predominate in the subendocardium, a region where the supply-demand imbalance is more significant during stress-induced ischemia. Ischemia delays the onset of shortening and reduces the speed and magnitude of systolic shortening, resulting in post-systolic shortening during isovolumic relaxation and decreasing the speed and magnitude of early diastolic lengthening.

The ischemia-induced reductions in the strain rate, the delay in the start of relaxation time, and the indices that assess the magnitude of post-systolic shortening have been the most useful parameters for detecting coronary artery disease.

The most current quantitative technique to assess myocardial deformation is speckle-tracking. Most of the studies focus on measuring longitudinal strain using apical views. Ischemia affects longitudinal strain earlier than radial strain. The systolic longitudinal, global strain is the most widely used quantitative parameter in most publications, identifying the ischemia.

The differences between different machines in the measurements are still under constant investigation and homologation attempt. Changes in blood pressure during the stress echocardiogram may influence strain values. An optimal parameter for the detection of ischemia by strain in the stress echocardiogram is not yet defined.

The stress echocardiogram's good accuracy detects coronary artery disease compared to coronary angiography as the gold. The imaging stress test is more accurate than the stress electrocardiogram, with 88 and a 93% specificity. Like all stress tests, detecting ischemic heart disease is higher in multiple vessels than in single-vessel disease.

Several meta-analyses found similar diagnostic accuracy of nuclear perfusion imaging and stress echocardiography, with the same sensitivity for detecting coronary artery disease, but the latter is more specific.

The stress echocardiogram is more sensitive than nuclear myocardial perfusion imaging for the left main coronary or multivessel disease. Other studies have shown similar sensitivity and specificity between the dipyridamole test and the dobutamine stress echocardiogram.[88]

The abnormal pressure response to stress does not reduce the accuracy of the echocardiogram. The abnormal wall motion during hypertensive response must render a positive stress finding.

The microvascular disease may affect wall mobility in the absence of significant epicardial coronary disease through several mechanisms that include microvascular abnormalities, endothelial dysfunction, vasospasm, small-vessel coronary disease, and amyloid deposition in intramyocardial vessels. Intensely false-positive stress echocardiograms may involve atypical and mid-ventricular segments as occurs in apical ballooning syndrome.

Microvascular disease, endothelial dysfunction, coronary small vessel disease, vasospasm, amyloidosis, and apical ballooning syndrome are differential diagnoses on false-positive stress echocardiograms.

False positives render a similar prognosis to true positives and justify intensive management of risk factors and strict clinical follow-up.

The stress echocardiogram discriminates patients at low risk from those at high risk to develop major cardiovascular events, including death. Simultaneously, negative results predict mostly benign prognosis, with event rate near to 0.9%/year, close to the normal population of the same age and the patients with normal coronary angiography. The course after a normal stress echocardiogram is similar to that of a normal myocardial SPECT (thallium 201, technetium-99 or sestamibi), with benign prognosis.

Compared with exercise stress echocardiography, dobutamine echocardiography is associated with a slightly higher risk of events, with older and sicker patients in the dobutamine group. The inability to reach the target heart rate on a dobutamine echocardiogram is associated with a higher event rate than patients with a negative test.[90]

According to multivariate analyses, the best predictors of cardiac events are peak

parietal mobility index and the left ventricle ejection fraction. In a study of 1500 patients undergoing stress echocardiography (3.4% exercise, 66% dobutamine) with a follow-up of 2.7 ± 1 years, 31% and 44% had a non-fatal myocardial infarction and cardiovascular death, respectively. A normal stress echocardiogram with parietal mobility index of 1 had a benign prognosis (0.9%/rate of cardiac events per year); the intermediate (1.1-1.7) and high indexes (1.7 or more, with 0.45 left ventricle ejection fraction or less), required additional risk stratification. The maximal stress parietal mobility index effectively stratified patients between low (0.9%/year), intermediate (3.1%/year), and high risk (5.2%/year) groups for cardiac events.

The extent and severity of wall motion abnormalities correlate with an increase in adverse cardiovascular events and are independent and cumulative prognostic predictors. The event rate ranges from a minimum of 0.9%/year in patients without wall motion abnormalities to a maximum of 6.7%/year in those with extensive wall motion abnormalities.

Another prognostic marker on the stress echocardiogram is the transient dilation of the left ventricle; resting LV volume and stress > 1.7 was the best threshold to define ischemic dilation. Patients with abnormal study and transient ischemic dilation have a greater extent and severity of parietal function abnormalities, higher parietal mobility index, multivessel disease probability, and more adverse events (19.7%) than ischemic patients without dilation (2.9%/year); this phenomenon is more observed in exercise stress echocardiography than in dobutamine echocardiography.[91-96]

MULTISLICE CT ANGIOGRAPHY OF CORONARY ARTERIES

The computed tomography coronary artery has clear evidence of benefit for coronary artery disease diagnosis in patients with chest pain. With the appropriate equipment and software, a good quality study allows evaluating the degree of obstruction and the plaque characteristics and helps identify high risk.[97]

The sensitivity of the study, on stable angina, is 97% (93-99% with 95% confidence interval) and its specificity is 78% (67-86% with 95% CI), for the detection of anatomically significant coronary artery disease. For functionally significant disease, its sensitivity is 93% (89-96% with 95% CI) and its specificity 53% (37-68 with 95% CI).[98]

The most important advantage of coronary CT angiography is its negative predictive value, which is 99%; a negative CT scan can rule out hemodynamically significant coronary artery disease with great certainty; this makes it a very useful test in low to intermediate patients pretest risk.[99]

Image quality is essential when performing a coronary angiography. The Society of Cardiovascular Computed Tomography (SCCT) ideally establishes having at least a 64-slice scanner. Significant obesity, difficulty in performing inspiratory apnea, inability to lift one or both arms, contraindication for beta-blockers, heart rhythm variation, nitroglycerine contraindication, risk of nephropathy, and elevated heart rate at rest should prompt to consider other diagnostic options.[100] Some protocols, technology, and acquisition adjustment allow reducing radiation.[101]

ASSESSMENT OF CHRONIC CORONARY DISEASE

Coronary CT angiography allows an objective evaluation of atherosclerotic plaque. Plaques classify as slightly, moderately, severely, heterogeneous or non-calcified. The Hounsfield units (HU) of the plaque may identify a high-risk, minimal luminal area, plaque load,[99] and degree of obstruction, qualitatively, and quantitatively according to the SCCT guidelines. The qualitative evaluation classifies:[102,103]

0 Normal: no evidence of plaque.
1 Minimum: plaque with minimal impact on lumen.
2 Mild: slight obstruction of the diameter.
3 Moderate: moderate stenosis and possible hemodynamic significance.
4 Severe: probable flow limitation.
5 Total occlusion.

The quantitative evaluation is similar and is divided into percentages: 0 Normal: absence of plaque and luminal stenosis; 1 Minimal: plaque with stenosis < 25%; 2 Mild: 25-49% stenosis; 3 Moderate: 50-69% stenosis; 4 Severe: 70-99% stenosis and 5 Occlusion: 100% stenosis.

The computed tomography angiography can rule out in-stent re-stenosis, especially in stents with larger diameters. Stents metallic artifacts difficult the diagnosis of patency, which may improve with some iterative reconstruction algorithms. Movement artifacts and partial volume effect also affect diagnosis.

The criteria for appropriate use consider the technology, the patient's characteristics, the time of implantation, and the site of stent placement, with the evidence that the larger the diameter of the stent increases the diagnostic precision.[104-107]

The provides information about arterial and venous grafts location, patency, and anastomosis sites; it also helps to evaluate the native vessels, with a different acquisition including a larger field covering the subclavian artery.[108,109]

The computed tomography fraction flow reserve is a post-processing tool, which does not require additional radiation or the administration of a pharmacological agent to induce stress,[110] being comparable to the obtained during cardiac catheterization,[111] with 86% sensitivity and 79% specificity for ischemia; a better predictor of major adverse cardiac events (MACE: death, non-fatal acute myocardial infarction, hospitalization, and unstable angina) at five years average follow-up, without long-term prognostic value yet. This test modifies the therapeutic management plan in two-thirds of the patients compared to angiotomography alone.[112]

The use of perfusion tomography is an imaging method that also increases the diagnostic accuracy of coronary angiotomography, performed at rest or after pharmacological stress, to evaluate myocardial ischemia; it requires several acquisitions, which increases the duration of the test. The current recommendation is to add myocardial perfusion by tomography in patients at high risk of ischemic heart disease.[113]

The coronary artery disease reporting and data system (CAD-RADS) standardizes the test report by communicating the findings and recommendations based on the results. Not only does it help to identify the severity of the disease, but it also identifies whether the patient has stents or vascular grafts, as well as high-risk plaque.[114]

In 1975 the American Heart Association established a system that assessed the coronary tree by dividing it into 16 segments that facilitates communication and clinical decision-making, using only the most severe identifiable obstructive lesion.[115]

The coronary calcium score (SCC) is one of the most important predictors of cardiovascular risk and has a superior predictive value to multiple algorithms, biomarkers, and screening imaging tests for cardiovascular disease. Coronary calcium is an early sign of coronary atherosclerosis; quantifying it allows determining therapeutic behavior changes in asymptomatic patients with low or intermediate risk.[116-118]

The test requires chest collimation, electrocardiographic gating in diastole, and at least five apnea seconds; it does not need contrast dye. The effective radiation dose is less than 1.0 mSv, similar to that of a mammogram.[119]

The coronary calcium, expressed in Agatston units (AU), results from a mathematical algorithm automatically calculated by software before manual validation of the lesions' location.

There are multiple cut-off points described to denote cardiovascular risk levels; in 15 prospective trials, the SCC of cero AU showed very low, 1-100 low, 101-400 intermediate, greater than 400 or percentile greater than 75% high, and > 1,000 very high risk.

Current evidence suggests that the greatest benefit is for individuals between 45 and 75 years old, with Framingham score intermediate-risk, since the SCC reclassifies approximately 50% of patients to low risk, minimizing costs, or high risk where statin therapy is recommended.[119-121]

NUCLEAR CARDIOLOGY

Nuclear instrumentation technology has shown great development for more than forty years

with proven efficiency of radionuclides and radiopharmaceuticals for diagnosis. At present, single-photon emission computed tomography (SPECT) is the most widely used nuclear imaging modality worldwide for coronary diagnosis. Most nuclear laboratories are equipped with multipurpose, variable angle detectors SPECT gamma cameras, as they allow imaging not only of the heart but any other organ.

There are also cardiology SPECT gamma cameras, with two 90-degree fixed-angle detectors and solid-state cardiology, with some of th e four universally accepted post-processing programs: Cedars-Sinai, Emory Tool Box, QGS/QPS, and Michigan 4D Corridor to share files and images with any similar diagnostic center in the world, and achieve minimal intra- and inter-observer variability.

Conventional cardiology gamma cameras are equipped, like the multipurpose ones, with detectors of Sodium Chloride activated with Thallium, which detect the electromagnetic energy of radioactive elements and convert it into electrical energy, then amplified through photomultiplier devices, and sent to workstations to create the images. However, cardiology gamma cameras significantly reduce the distance between the heart and the detectors, achieving a lower percentage of artifacts due to tissue attenuation.

Solid-state gamma cameras (with high-efficiency Cadmium, Zinc, and Tellurium detectors' high radiation count, motionless acquisitions, and extreme proximity to the patient's chest), reduce the dose of radioactive drugs and artifacts, improve image quality and diagnostic performance and estimate the absolute coronary blood flow, previously reserved only for positron emission tomography (PET).

Thallium-201, and Sestamibi, and Tetrofosmin labeled with Metastable Technetium 99 (Tc99m) are the currently accepted radionuclides for myocardial perfusion. Thallium-201 undergoes redistribution, the gradual incorporation into a living but critically hypoperfused tissue, making it ideal for identifying myocardial viability after reinjection.

Radiopharmaceuticals labeled with Tc99m do not show redistribution and are highly dependent on coronary blood flow, making them convenient to confirm or rule out ischemia.[122,123]

SPECT performed myocardial perfusion tests offer several types of images. The tomograms display in two rows that correspond to stress and resting, in two longitudinal axes, vertical and horizontal, and short or transverse. The evaluation of the degree of ischemia is merely qualitative, and the same happens in the three-dimensional images of the left ventricle.

The unification of the reporting criteria, displays the ischemia quantification in polar maps, promoted by the multicenter study «Ischemia Trial», constructed by short-axis tomograms, from the apex to the left ventricular base, both under stress and at rest. The ischemia degree comes from the summed differential score, resulting from the difference between the summed stress score and the rest. Other images and data derived from SPECT are those of the function, timing, contractility, ventricular dilatation and the incorporation of radionuclides into the lungs, meaning elevation of LV end-diastolic pressure and significant functional deterioration.[124]

According to the polar maps, if there is no reversibility, the study is negative for ischemia; if the reversibility ranges from 1 to 9%, it is mild; for 10 to 14% moderate, and 15% or more, it is severe. The left anterior descent coronary is involved when the ischemia is in the anterior wall, interventricular septum, apex; the left circumflex for the lateral wall, and the right for the inferior wall. The clinical aspect of the patient and the electrocardiographic changes should complete the nuclear perfusion assessment.

SPECT's diagnostic efficiency of myocardial perfusion tests was determined compared to the results of invasive coronary angiography, disclosing 87% sensitivity and 73% specificity, adding pharmacological stress, dipyridamole or adenosine, the sensitivity reaches 89%, and specificity 75%, with conventional gamma cameras. With solid-state cardiology gamma cameras and CZT detectors, the sensitivity goes to 95%, with similar specificity.[125,126]

This test identifies ischemia, but not necessarily atherosclerosis origin; other causes are left ventricular hypertrophy, coronary artery ectasia, muscle bridging, anomalous congenital origin, and microvascular dysfunction. The high

sensitivity renders a high negative predictive value; if the study indicates no disease, the probability of a false negative result is remote. Hence, the post-test probability of an acute coronary event is less than 1% at four years after a negative result.

However, specificity is not prominent, rendering false-positive results, not worse than false-negative ones. Finally, all these factors influence the type of indication and reference level and how inadequate, uncertain, or adequate it is to carry out a myocardial perfusion SPECT test.[127,128]

The 2003 North American consensus established three indications for nuclear cardiology tests:

1. Acute ischemic syndromes.
2. Chronic ischemic syndromes.
3. Heart failure (myocardial viability).

The 2005 Mexican Institute of Social Security (IMSS) made a similar consensus, confirmed in 2011, for five indications:

1. Identification of silent myocardial ischemia.
2. Suspected myocardial ischemia.
3. Risk stratification.
4. Acute coronary syndrome.
5. Identification of myocardial viability.

More than 70% of ischemic episodes are silent, hence the importance of identifying it to decrease fatality, especially for those with a family history of coronary heart disease, dyslipidemia, and premature cardiac death as well as subjects with metabolic syndrome, mainly diabetes mellitus, and those with professional risks, such as aviation pilots and operators of various means of transport.[129,130]

The lethal cardiac ischemia has not decreased in our country and many others throughout thirty years, after failed strategies. New cardiovascular drugs, thrombolysis, coronary artery intervention, and technological advances in all imaging modalities, non-invasive or invasive, failed in reducing morbidity and mortality. So, prevention, risk factors modification, and early and timely diagnoses are possibly the only solution.

The nuclear cardiology department controls the biases derived from the pharmacological stress test, stress test's performance, acquisition, processing, interpretation reporting of the result. The patient referral is the only bias beyond its control; hence the importance of following clinical practice and consensus guidelines. The subject correctly sent to myocardial perfusion studies should not have a low or high probability of having CAD, but rather intermediate, to define next steps, based on the ischemia degree. The 2013 consensus of all North American non-invasive and invasive cardiovascular imaging and cardiology societies established the pre-test probability for coronary heart disease as follows:[131,132]

1. Low pre-test predicts less than 10%.
2. Intermediate pre-test predicts between 10 and 90%.
3. High pre-test predicts more than 90%.

The thallium-201 SPECT with reinjection, in two-phase at rest, or a PET with fluorine-18-deoxyglucose, distinguish ischemia, stunning and hibernation; reversible conditions, different from myocardial dead.[133]

Most patients with severe myocardial damage die of ventricular arrhythmia; the isotope tests determine if there is any possibility of recovery, even partially, after revascularization.[134]

Nuclear cardiology, in its SPECT modality, offers a fully discriminative diagnosis. Various diagnostic methods and non-invasive imaging determine the probability of suffering CAD; they are calibrative since they establish a risk, but not whether the disease exists or not. Radionuclide myocardial perfusion images allow quantitative analysis of myocardial perfusion and left ventricular function.

The heart studies with positron emission tomography (PET) are a useful tool for the diagnosis of chronic ischemic heart disease (IC). PET allows quantification of in vivo physiological and pathophysiological processes of the heart through high-energy molecular radiotracers with a short physical half-life (T½). These radioisotopes are positron emitting that resemble natural processes at the molecular

level and characterize physiological processes in qualitative and quantitative terms.[135]

The most common in clinical practice are rubidium-82 (82Rb; T½ 75 sec) or nitrogen-13-ammonia (13 NH3; T½ 10 min) for perfusion, and 18F-fluoro-2-deoxyglucose (18 FDG; T½ 110 min) for viability. An external detector system acquires the tomographic images, adding simultaneous non-invasive anatomy of the coronary arteries by computed tomography (CT), through hybrid equipment (PET/CT), which combines in a single technology the anatomical (CT) and functional (PET) evaluation of coronary artery disease (CAD).

The acquisition of PET tests gates to the electrocardiogram (Gated-PET) simultaneously evaluating left ventricular function adds prognostic value. Although its availability is increasing in our country, sometimes its cost limits its utilization. PET has higher sensitivity and spatial resolution than SPECT, mainly in specific groups such as multivessel epicardial coronary disease, obesity, women, and microvascular dysfunction.[136]

Another advantage of PET is low radiation exposure (82Rb: 3.5 mSv, 13 NH3: 1.5 mSv, 18FDG: 7mSv), which is significant due to the lower dose and shorter half-life. PET has a place in evaluating myocardial perfusion (ischemia), energy metabolism (viability), and quantifying regional and total myocardial blood flow.[137]

The acquisition of images at rest and stress after the administration of 13 NH3 or 82Rb has high diagnostic efficiency detecting myocardial ischemia, with 90% (95% confidence interval [CI]: 83-100%; $p < 0.05$) sensitivity to detect 50% stenosis in at least one vessel and 89% (95% CI: 75-100%; $p < 0.01$) specificity; 94% (95% CI: 80-100% $p < 0.01$) positive predictive value and negative predictive value (NPV) (95% CI: 85-98%, $p < 0.01$); with 100% diagnostic efficacy.[138]

The sensitivity to detect single-vessel CAD is 92% and 95% in multivascular disease, respectively. Due to its high spatial resolution, the images obtained in obese patients or increased breast tissue show less attenuation (attenuation artifact). In this group of patients, the sensitivity to detect obstructive coronary disease is very high, up to 100%.[139]

The evaluation of multivascular disease, with or without previous infarction, requires special attention since often only perfusion alteration is discovered in the coronary territory of the most severe or significant stenosis, because the vasodilator reserve is abnormal, even in the presence of noncritical stenosis, reducing flow heterogeneity and myocardial perfusion abnormalities.

Significant left-main or multivascular injury can lead to a steady-state in the myocardial flow distribution (homogeneous), so perfusion may appear normal. In these cases, the Gated-PET (rest/stress) and the left ventricular function assessment (transient dilation under stress, end-diastolic/end-systolic volume increase, stress ejection fraction decrease, parietal mobility alterations, and systolic thickening decrease) add prognostic value.[140,141]

The simultaneous evaluation of myocardial perfusion and ventricular function increases the identification of high-risk patients (85%), with a greater probability of developing cardiovascular events at one year (5-7%), compared to those of low risk (< 1%). PET studies for diagnosis and risk stratification of myocardial ischemia works in patients with moderate-high pretest risk for a functional assessment of anatomic coronary stenosis.

PET images with 13 NH3 at rest/stress allow a non-invasive, absolute, and dynamic quantification of myocardial blood flow at rest (FMR), myocardial blood flow at stress (FME)(quantified in mL/min/g of the myocardium), and coronary flow reserve (CFR = FME/FMR); the latter the most important prognostic variable.

The measurement of the regional and global flows interprets the functional repercussion of coronary stenosis.

The values obtained are usually linear and inversely proportional to stenosis severity, mainly when > 80%. The determination of myocardial flows has an important role in the identification of high-risk patients with multivascular disease with normal or minimally abnormal perfusion; in these cases, most patients have an abnormal CFR (< 2.0); on the opposite, a preserved CFR (> 2.0) confers a low probability of left-main or multivascular disease (NPV 97%).

A homogeneous decrease in CFR in the three coronary anatomical territories can detect diffuse endothelial damage and or microvascular disease. Quantification of myocardial flows and CFR is also a prognostic tool for major cardiac events. Patients with preserved CFR (> 2.0) have a good prognosis (cardiovascular events and death < 1% per year), compared to those with decreased CFR (< 2.0) (> 5-7% per year).

A CFR < 1.6 renders a worse prognosis and suggests significant diffuse disease. The determination of myocardial flows plays an important role in diagnosing and risk stratification of patients with microvascular diseases, such as those with chronic kidney disease, post-transplant vasculopathy, women, and diabetics.[142]

Studies with 18 FDG have shown greater utility in those patients with dilated cardiomyopathy of ischemic origin and < 35% ejection fraction for myocardial viability. The protocol for viability (perfusion-metabolism) includes the evaluation of baseline perfusion (perfusion images at rest with 13 NH3) and images at rest with 18 FDG (energy metabolism or viability), obtaining four main diagnostic patterns:

1. Normal: preserved perfusion and metabolism.
2. Discordant or «mismatch»: the hibernating myocardium is characterized by impaired myocardial perfusion at rest and preserved metabolism. Greater discordance (viability) suggests ventricular function improvement after revascularization, in the regional presence of 5-7% viable myocardium, and notable survival improvement on 25% (25-40%).
3. Concordant or «match»: the presence of abnormal myocardial perfusion and abnormal metabolism. This pattern indicates scar (infarction) without viable tissue, predicting poor improvement and survival after revascularization.
4. Reverse discordant or «reverse mismatch»: normal perfusion and decreased metabolism present in special situations: non-ischemic cardiomyopathy, myocardial stunning, left bundle branch block, and some patients with diabetes mellitus.

The 18 FDG protocol has 92% sensitivity and 68% specificity for myocardial viability (discordant pattern) to predict improvement after revascularization.

In the presence of abnormal segmental mobility, the detection of «discordant» patterns highly predicts the existence of reversible and recoverable segments after myocardial revascularization in up to 85% of cases. Those patients with evidence of viability who do not undergo revascularization are more likely to experience major cardiovascular events (myocardial infarction, death, and heart failure) against revascularization ($p < 0.01$).[143,144]

Therefore, viability studies with PET predict outcome in patients with dilated cardiomyopathy of ischemic origin (< 35% ejection fraction).[145]

In summary, advances in non-invasive molecular imaging, especially in the cardiovascular area, currently allow a comprehensive and detailed assessment of the function, energy metabolism, and cardiac vasculature. 18FDG PET studies are currently the gold standard for detecting myocardial viability in nuclear cardiology, providing additional information in patients with dilated cardiomyopathy of ischemic origin, complex therapy, and high revascularization risk.

The simultaneous study of physiology (perfusion, myocardial flows, energy metabolism) and coronary anatomy using hybrid techniques with PET/CT offers a complete evaluation of coronary atherosclerosis functional repercussion.[146-150]

MAGNETIC RESONANCE IMAGING

Cardiovascular magnetic resonance imaging (CMR) is a non-invasive and ionizing radiation-free test to evaluate cardiovascular diseases' etiology due to its ability to estimate function, edema, perfusion, and fibrosis. CMR is also useful to assess the presence of ischemia and viability of the myocardium in patients with heart failure and chronic ischemic heart disease. These patients usually present segmental alterations in contractility and ventricular dysfunction due to stunned or hibernating myocardium, with recovery potential after coronary revascularization.

The detection of myocardial viability may predict benefit from revascularization under late gadolinium-enhanced CMR, indeed II-b recommendation of the European Society of Cardiology for evaluating myocardial ischemia and viability in patients with coronary artery disease and heart failure with reduced ejection fraction.[151]

The MR-INFORM study compared fractional flow reserve (FFR) vs CMR perfusion in patients with stable angina and an intermediate-high probability of coronary artery disease, with the primary outcomes of death, non-fatal MI revascularization in one year. CMR was not inferior to FFR concerning the primary cut-off points; however, patients with CMR had less revascularizations (162 [35.7%] vs 209 [45.0%], p = 0.005).[152] Meta-analyses showed that myocardial perfusion stress studies with magnetic resonance imaging, computed tomography, and positron emission tomography can accurately rule out hemodynamically significant coronary artery disease against FFR as a reference standard, wit 90% sensitivity and 85% specificity [3]. However, these studies have different cut-off points for stenosis (≥ 50 and 70%) and equipment (1.5 T and 3 T).[153,154]

Dobutamine CMR can detect ischemia-induced abnormalities in wall motion, comparable to dobutamine stress echocardiography, particularly useful in suboptimal acoustic windows and contraindication to adenosine. In patients with chronic ischemic heart disease, it provides a strong orientation towards revascularization if the result is positive. If it is negative, it can also provide important information on the underlying pathophysiology (microvascular or inflammatory disease such as myocarditis), which may explain the symptoms and guides specific medical treatment.[155]

The 2019 guidelines on criteria for the appropriate use of multimodal imaging in evaluating cardiac structure and function in nonvalvular heart disease considered CMR appropriate to exclude coronary artery disease in patients without angina with heart failure or ventricular dysfunction and to decide on intracardiac defibrillator/resynchronization therapy after revascularization.[156]

Cardiac MRI with adenosine/dipyridamole images under adenosine stress (140 µg/kg per minute) and at rest, during the injection of 0.1 mmol/kg gadolinium at three short-axis locations renders 89% sensitivity and 85% specificity.[157]

Gadolinium may cause nephrogenic fibrosis in patients with advanced kidney disease. T1 mapping is a promising non-contrast technique that allows for quantitative characterization of tissue since, under normal circumstances, adenosine's vasodilator stress causes an increase in myocardial blood volume and, consequently, an increase in myocardial T1. Mapping of T1 at rest and adenosine stress can help differentiate normal, ischemic, and infarcted myocardium; however, prospective studies are still required to evaluate this technique.[158,159]

The STRATEGY study compared CMR against CT in 600 symptomatic revascularized patients, finding that the patients who underwent CMR had less major cardiac adverse effects, cost, need for other imaging studies, and invasive angiography. Stress CMR continues underused in our country, even though several studies in other countries demonstrate lower cost,[131] perhaps due to low availability of equipment and lack of adequate software for analysis and acquisition in public and private institutions.

The American College of Cardiology criteria considers perfusion CMR appropriate on the intermediate probability of cardiovascular disease and nondiagnostic stress ECG and high probability of ischemic heart disease, regardless of the exercise ECG result. CMR can also recognize the cause of chest pain in patients with a low probability of ischemia (myocarditis, pericarditis, or microvascular disease), easily missed on invasive coronary angiography or computed tomography. However, it is not the best to evaluate ventricular function in patients with SICA.

Cardiac MRI can find the cause of troponin elevation in 87% of cases without coronary obstructions. The most frequent causes are myocarditis, apical hypertrophic cardiomyopathy, acute myocardial infarction, and *tako-tsubo* cardiomyopathy.[160]

ISCHEMIC HEART DISEASE IN WOMEN

The diagnostic approach to ischemic heart disease has continuously changed due to

current knowledge about the difference between genders.

The recognition of the behavior of the various traditional and the emergence of new risk factors unique to gender, or predominant in women, could allow a restratification of cardiovascular risk and, in turn, predict that patients will eventually develop cardiovascular disease.[161]

Until now, the diagnosis of ischemic heart disease in women follows the definition of typical angina, derived from the result of the analysis of large male populations, and by the tendency to emphasize therapeutic strategies for the obstructive coronary disease.[162]

The diagnosis is more difficult in women than in men. It is common to observe that women have different symptoms, with pain in places other than the precordial or retrosternal region, like the lower jaw, arms, neck, shoulders, back, and epigastrium, and angina equivalents such as dyspnea, palpitations, presyncope, fatigue, sweating, nausea, or vomiting.[163]

Atypical angina is more common in women with suspected ischemia related to coronary obstructions than typical angina and predicts higher long-term mortality; perhaps this would explain the worse prognosis in women due to less recognition of angina.[164]

The typical symptoms for coronary obstructions usually occur in older women, but not in young women. Instead of occurring on exercise, atypical symptoms occur at rest, associated with fatigue, or emotional stress, particularly periods of mental stress, which even wakes her up at night, and is a simple trigger for ischemia, likewise they occur more often during daily activities, and not when exercising. The psychosocial origin is a true trigger for ischemia that causes angina in women, which may have implications for management and prognosis.[165]

Diamond et al. described three criteria (retrosternal location, relationship with exercise, and disappearance with rest or nitroglycerin) in 1979, later called typical angina if it has all three characteristics, atypical angina if it has two, and non-anginal chest pain for only one or none. The vast majority of women have a probability of less than 15% coronary obstructions with only dyspnea or typical or atypical angina. The pretest probability increases above 15% in women with atypical angina after 70 years and in women with typical angina after 60 years old.[166]

Up to 60% of coronary angiographies are negative. A Mexican review of patients referred to cardiac catheterization observed that up to 43.5% of women did not have obstructive lesions; 19% of men presented this condition. The proportion of positive nuclear medicine tests (14 vs 16%) and stress electrocardiogram was similar (36 vs 28%).[167]

The biggest problem is that patients with non-obstructive arterial disease and angina symptoms have multiple hospital admissions and reevaluation for non-obstructive coronary disease, with angina persistence in approximately 50% of patients.

Recurrent angina is associated with non-fatal myocardial infarction, cerebrovascular disease, lower functional capacity, and chronic angina. Women with angina without coronary obstructions are at increased risk of hospitalization mainly due to stable, unstable angina, new revascularization procedures, and heart failure, compared to healthy controls.[168]

Appropriate diagnostic evaluation is the first step towards improving the prognosis of women with known ischemic heart disease, with identification of patients with varying degrees of risk, the various diagnostic tests according to physical status and pretest probability, in agreement with the consensus of the American Heart Association, which defines the role of non-invasive tests in the clinical evaluation of women with suspected ischemic heart disease.

There are many very important studies in favor of treating women with chronic ischemic heart disease. There is always a great debate about revascularization indication, considering the patient's specific profile, including diabetes, previous revascularizations, number of affected vessels, ejection fraction, and comorbidities. However, the question is whom to select for cardiac catheterization, when and what studies help make this decision, and support the clinical context to avoid leaving out of catheterization and potential timely revascularization.

The basis of everything is the clinic, the risk factors, and the pretest probability of coronary disease. The guides are very clear about what to do, but the behavior varies according to

places and context, mostly available resources, equipment, and expertise.

The objective of studying a patient with ischemic heart disease aims at detecting ischemia, its extension, and its relationship to the coronary anatomy; the combination of different tests can come close to this ideal.[169-171]

CORONARY DIAGNOSIS ON ATRIAL FIBRILLATION

Atrial fibrillation imposes considerable difficulty to detect myocardial ischemia due to the lack of appropriate rate response to exercise or drugs; this is a significant problem because this arrhythmia is becoming more frequent with the population age.

Bouzas-Mosquera et al. published their results in 419 patients with atrial fibrillation referred for chest pain to exercise-echocardiogram; many of them under chronotropic modification (beta-blockers, calcium channel blockers, and digoxin). Ninety percent of the patients performed Bruce protocol, and 13.6% did not reach age-predicted maximal heart rate. The study aimed to follow up the patients, 31 ± 3 years, for prognosis; they did not compare against other ischemia-detecting tests.

The result of this publication is quite interesting in terms of prognosis because the combination of resting wall motion abnormalities and ischemia was associated with 55.7% five-year risk major cardiac events, compared with 10.3% in patients without resting or exercise-induced wall motion abnormalities ($p = 0.001$).

This publication is useful to know the importance of detecting myocardial ischemia in atrial fibrillation, besides its well-known worst cardiovascular prognosis.[172] The myocardial perfusion imaging on cadmium-zinc-telluride camera renders comparable diagnostic accuracy on atrial fibrillation, compared to matched sinus rhythm controls, but only under dipyridamole provocation ($p = 212$). The test has very poor accuracy under exercise provocation.

The cardiac magnetic resonance with inducible ischemia, under adenosine or dipyridamole and late gadolinium enhancement, gives a good quality image and accuracy for prognosis of major cardiovascular events (8.9 versus 1.2%; hazard ratio HR 7.56; 95% confidence interval CI: 4.86-11.80; $p < 0.001$). The results compare well against catheter-based coronary angiography.[173]

CORONARY DIAGNOSIS ON LEFT BUNDLE BRANCH BLOCK

The left bundle branch block (LBBB) is a significant precedent that impacts the patients' prognosis, especially if coincident with mild to moderate reduction of the left ventricle ejection fraction.[174]

LBBB is an obstacle when trying to unmask myocardial ischemia due to the very poor electrocardiographic value and its associated septal motion delay. The dobutamine stress provides over 90% accuracy for ischemia in the left circumflex territory and 82% sensitivity for ischemia in the left anterior descent coronary artery territory.[175-177]

As echocardiography, nuclear perfusion imaging has more accuracy with pharmacologic than exercise stress; nonetheless. The confounding septal perfusion results may improve with PET instead of SPECT. The heterogeneous regional radionuclide uptake in LBBB is related to underlying regional myocardial dyskinesis and wall thickness rather than stress-induced ischemia.[178-180]

The computed tomography coronary angiography has a similar value for patients with LBBB and patients without it. This test may completely rule out significant coronary stenosis, especially in patients under 65 years old. For older patients, this test has the usual limitations due to calcifications.

The 64-slices tomography or more can assess the coronary anatomy, showing accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 64-slice CT for identifying coronary artery disease, was 95, 97, 95, 93, and 97%, respectively, and by segment was 97, 72, 99, 91 and 97%, respectively.

Finally, the cardiac magnetic resonance compares favorable against echocardiography, both under dobutamine stress, with the same sensitivity (72%), but higher specificity, negative predictive value, and overall diagnostic accuracy than did DSE (87.5

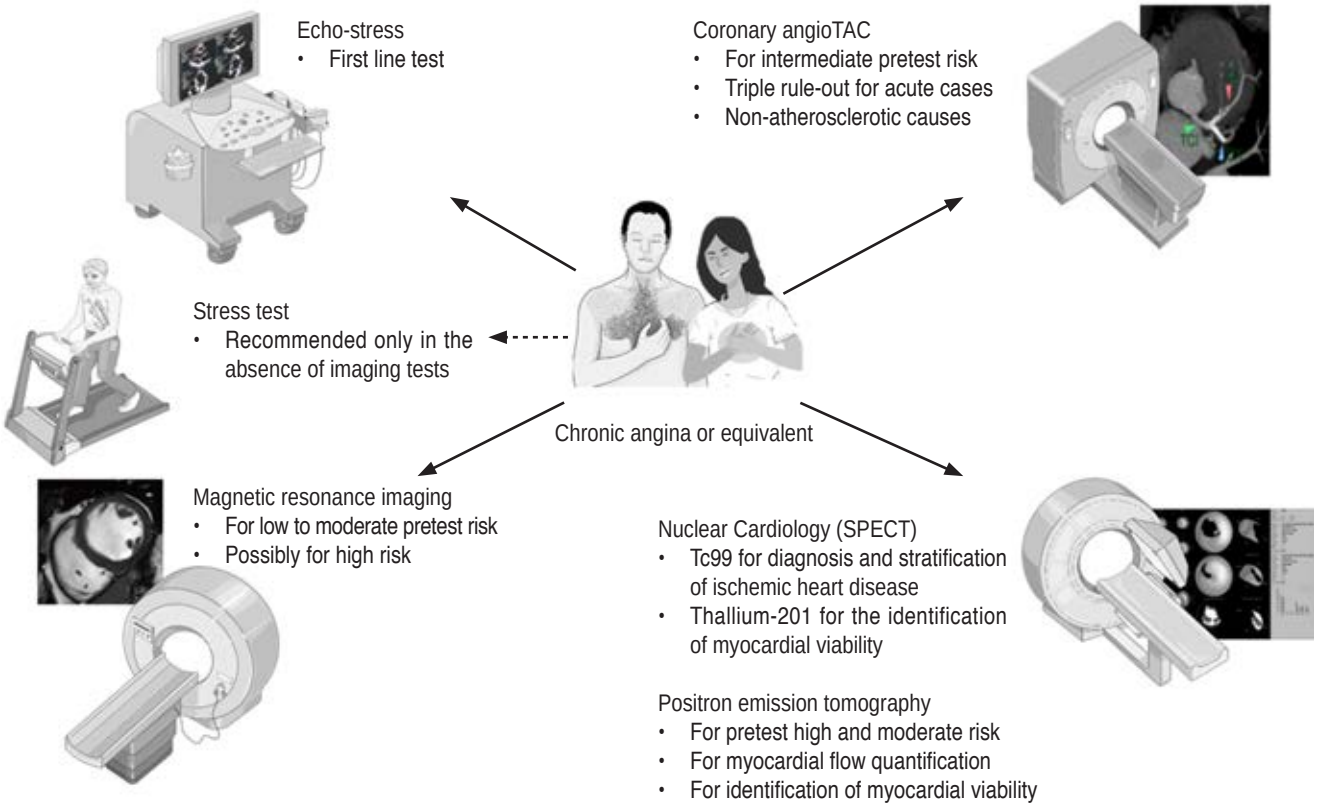

Figure 1: Flow chart with the consensus recommendations for the diagnostic approach to the chronic coronary artery disease.

vs 72.9%; 80.8 vs 67.3%; and 80.4 vs 72.0%, respectively), and further improved sensitivity (82.4%), specificity (95.8%), positive predictive (93.3%), negative predictive value (88.5%) and diagnostic accuracy (90.2%) with first-pass stress perfusion and late gadolinium enhancement.[181-183]

CONSENSUS RECOMMENDATIONS

Figure 1 summarizes the consensus recommendations about non-invasive tests.

1. The consensus discourages to rule out coronary disease based solely on symptoms and signs.
2. The term non-typical angina must be separated from clinical history since it automatically excludes the disease and generates diagnostic errors.
3. The consensus recommends abolishing the male gender as a significant coronary risk factor in the medical charts; both men and women have equivalent risks after the estrogenic vascular protection ends.
4. The consensus recommends careful follow-up in transgenders under hormonal therapy for early onset of atherosclerotic complications, including coronary heart disease.
5. The consensus recommends stress electrocardiogram only under image tests unavailability, intermediate pretest probability, and maximal stress test. Always stating that stress electrocardiogram does not rule out coronary heart disease.
6. The consensus recommends the stress echo as one of the first-line diagnostic approaches for chronic coronary disease, with a preference of exercise, when possible.
7. The consensus recommends the computed tomography coronary angiography:
   a. In patients with intermediate pretest risk, with appropriate equipment.

   b. to evaluate chest pain in the emergency room in intermediate-risk and non-interpretable electrocardiogram.
   c. In selected acute chest pain cases, for triple rule-out protocol decision (coronary stenosis, pulmonary embolism, and aortic dissection).
   d. For non-atherosclerotic causes of ischemic heart disease, such as abnormal origins of the coronary arteries, ectasia, and muscle bridges. It is the best method to establish the spatial relationship between the coronaries and neighboring structures.
   e. Special caution in patients with arrhythmias (especially atrial fibrillation) and high heart rates difficult to reduce with negative chronotropic drugs as this may affect the image quality.
   f. Not indicated in renal failure without replacement therapy; consider deferral in the case of risk of contrast dye induced nephropathy.
   g. The requesting physician must prepare the patient, mainly with the use of negative chronotropic medications, take care of the use of medications that can facilitate kidney damage by contrast medium, and guarantee sufficient apnea.
8. The consensus recommends labeling Tc99m for diagnosing and stratifying myocardial ischemia and reserve Thallium-201 to identify viability in the cases with significant ventricular dysfunction and possible revascularization.
9. The consensus recommends the PET test in:
   a. Patients with moderate-high pretest risk, for functional evaluation, after a non-diagnostic coronary angiography.
   b. Patients with abundant breast tissue or prosthesis, or other image quality attenuation.
   c. Suspected tri-vascular or left main coronary disease.
   d. Suspected microvascular disease.
   e. Suspected post-heart transplantation vasculopathy.
   f. Ischemic dilated cardiomyopathy for revascularization suitability.
10. The consensus recommends the perfusion cardiac magnetic resonance:
   a. In patients with a low to intermediate pretest probability, a negative perfusion CMR carries a good prognosis and often identifies the underlying noncoronary cause of the patient's symptoms.
   b. In patients with an intermediate to high pretest probability of CAD, the current invasive strategy is the most appropriate, but stress CMR is an option.
   c. CMR helps recognize the cause of chest pain in patients with low pretest probability and patients with negative troponin-positive coronary angiography.
11. The consensus discourages any exercise test from inducing myocardial ischemia on patients with atrial fibrillation or LBBB.
12. The consensus recommends, on patients with atrial fibrillations, to diagnose myocardial ischemia with CMR under adenosine or dipyridamole and late gadolinium enhancement or dipyridamole myocardial perfusion imaging on cadmium-zinc-telluride camera.
13. The consensus recommends, on patients with LBBB, to diagnose coronary heart disease with $\geq$ 64 slices of computed tomography in patients under 65 years old; beyond that age, calcification may reduce the specificity.
14. The consensus recommends that patients with LBBB diagnose myocardial ischemia with either echocardiography or nuclear scan under pharmacological stress. In the case of nuclear scan; the consensus recommends PET over SPECT.
15. The consensus recommends, on patients with LBBB, dobutamine-induced myocardial ischemia and gadolinium enhancement.
16. The consensus does not recommend cardiac catheterization, in chronic coronary disease, without evidence of ischemia, moderate to severe impairment of the lifestyle, or coronary or hemodynamic instability.

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