Universitat de Girona
Facultat de Medicina

The role of dipyridamole-exercise echocardiography test for diagnosis of coronary artery disease.

Future challenges and prospects

Final degree project

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Vull expressar la meva gratitud a tot el departament

d'imatge cardíaca de l'Hospital Josep Trueta, on he après moltíssim i,

on m'he sentit molt acollida durant les meves pràctiques al servei.

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que m'han guiat en tot moment per poder realitzar aquest projecte.

Mil gràcies.

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ABSTRACT

Background: Coronary artery disease (CAD) is the third leading cause of mortality worldwide and the first cause of death in the Spanish state (1). It has been well documented that exercise stress test using electrocardiographic and echocardiographic markers of ischemia, most of the time, allows the non-invasive detection of CAD (2). Even so, a significant proportion of patients with a history of chest pain are still unclassified, without an objective diagnosis of ischemia, with all the consequences that this entails.

In this patient population, the use of a combined stress (physiological with exercise plus pharmacological with dipyridamole) could provide greater sensitivity for the diagnosis of CAD.

Dipyridamole can reduce myocardial oxygen supply through flow maldistribution and increased dynamic stenosis (3). On the other hand, exercise increases myocardial oxygen demand considerably, but it can simultaneously cause an increase in dynamic stenosis (4).

The theory is that the two types of stress could act synergistically to cause an imbalance between myocardial oxygen demand and supply.

Objective: The purpose of this study is to evaluate whether dipyridamole infusion to exercise stress echocardiography allows the identification of a significant proportion of patients with CAD, where exercise-only echocardiography is inconclusive.

Design: A cross-sectional study in the cardiac imaging unit of the Hospital Universitari de Girona Doctor Josep Trueta.

Methods: patients who have undergone exercise stress echocardiography, on suspicion of CAD and inconclusive result, will perform the same test again but adding dipyridamole, with the aim of diagnosing a significant proportion of patients with CAD. This cross-sectional study will be carried out in 1 and a half year in Girona.

Keywords: Coronary artery disease, ischemia, chest pain, exercise stress echocardiography, dynamic stenosis

ABBREVIATION LIST

CAD. Coronary artery disease

CVD. Cardiovascular Disease

COPD. Chronic obstructive pulmonary disease

MI. Myocardial infarction

AHT. Arterial hypertension

LDL-C. Low-density lipoprotein cholesterol

ACS. Acute coronary syndrome

CCS. Chronic coronary syndrome

ACE. Angiotensin-converting enzyme

HF. Heart failure

LV. Left ventricular

CT. Computerized Tomography

PCI. Percutaneous coronary intervention

CABG. Coronary artery bypass grafting

RCA. Right coronary artery

LAD. Left anterior descending

Cx. Circumflex

SPECT. Single photon emission computed tomography

AV. Atrioventricular

AHA. American Heart Association

1. INTRODUCTION

1.1 CORONARY ARTERY DISEASE

1.1.1 DEFINITION

Ischemic heart disease, also called coronary artery disease (CAD), is a clinical syndrome characterized by coronary atherosclerosis and different degrees of myocardial ischemia, which leads to acute (acute coronary syndrome) and chronic (stable angina) processes and is also the most common cause of heart failure (5).

1.1.2 PATHOPHYSIOLOGY

The phenomenon that best explains the process of atherosclerosis is endothelial dysfunction. In this, there is loss of the regulating function of vasomotor tone, the adhesion of platelets to the endothelial surface is facilitated, monocytes tend to be attracted, and their passage through intercellular junctions is facilitated, the membrane becomes more permeable to passage of LDL cholesterol and fibrinolytic function is inhibited (6). This process entails an accumulation of abnormal material (macrophages, foam cells, cholesterol deposits...) on the walls of the arteries and that generates a progressive decrease in arterial calibre (5). When the atheroma plaque reaches a significant degree of stenosis (more than 50%), it produces a fixed obstruction of blood flow, therefore, in conditions of decreased oxygen supply to the myocardium (anaemia, hypoxemia, hypotension) or increased of myocardial oxygen demand (physical exercise, tachycardia), there is an imbalance between supply and demand of O2 that causes angina (retrosternal pain of an oppressive nature) (7). Then, angina is caused by myocardial ischemia, without cell necrosis.

Stable angina, the most common type, develops during physical activity and usually lasts until the end of that activity. On the other hand, unstable angina usually occurs at rest.

When blood flow to the heart muscle is completely blocked by the rupture of the atheroma plaque, cardiomyocytes die, causing an acute coronary syndrome (ACS) (5).

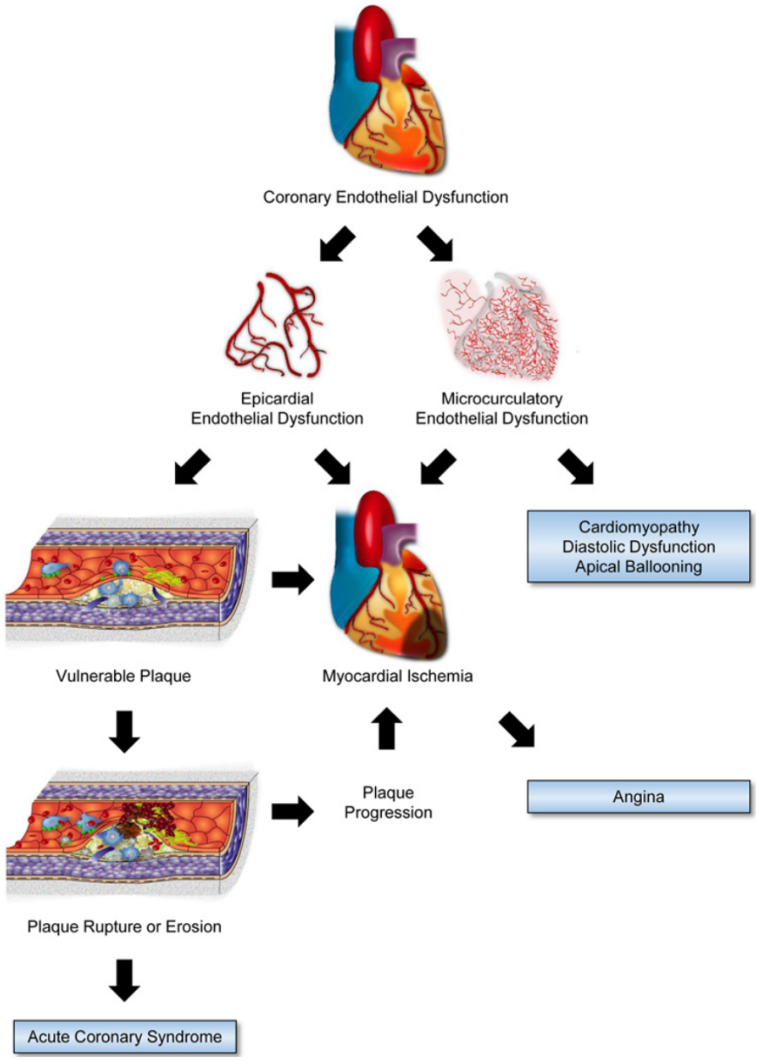

Figure 1. Endothelial dysfunction in CAD. Extracted from (8).

Simultaneously, atheroma plaques with stenosis between 30 and 60% are more frequently vulnerable plaques, that is, with characteristics that make them more prone to thrombotic complications and a consequent ACS.

On the other hand, the lesions with greater obstruction (more than 75%) are usually stable plaques, with greater resistance to plaque rupture and, therefore, less risk of thrombotic complications. Vulnerable plaques can also stabilize, either spontaneously or with medical treatment (6,8).

1.1.3 EPIDEMIOLOGY

Ischemic heart disease remains the most important cause of premature mortality, a major cause of disability and the third leading cause of mortality worldwide (1). CAD accounts for approximately 610,000 deaths annually (estimated 1 in 4 deaths).

In Europe, there are more than 4 million deaths each year from CAD. This corresponds to 45% of all deaths; 49% among women and 40% among men. In particular, twice as many men than women under the age of 75 years die from CAD.

In Spain, ischemic heart disease is the leading cause of death in men and cerebrovascular diseases the leading cause of death in women (53). The incidence rates of acute myocardial infarction in Spain range between 135-210 new cases per year for every 100.000 men and between 29-61 per 100.000 women between 25 and 74 years of age (9,10).

The aging of the population, together with the decrease in mortality in the acute phase, means that there are more and more patients with this pathology, which implies a great healthcare and economic burden for Western health systems. It is estimated that in Spain the global cost of treatment for the first year of patients suffering from ACS is around 1 billion euros. (11,12).

While CAD is a significant cause of death and disability, it is preventable. The decline in CAD mortality rates in developed countries has largely been due to addressing political, economic, and social determinants, control of major cardiovascular risk factors, and improved acute and chronic care (13).

1.1.4 CARDIOVASCULAR RISK FACTORS

The risk factors for cardiovascular diseases are related to the personal characteristics, lifestyle habits or other health problems of each individual that can damage the arteries and cause arteriosclerosis (5).

Age: The increased risk of CAD is significant in men older than 45 years and women older than 55 years (14). Women before menopause have oestrogens that exert a cardioprotective effect (15).

Genetics: A family history of angina or infarction may imply a genetic predisposition. Family members of men under 55 or women under 65 who have suffered an infarction, increase the risk (16).

Smoking: this increases death from coronary disease by about 70%. This risk is intimately related to the intensity and duration of the smoking habit. Even passive smokers have an increased risk of cardiovascular disease. The cessation of tobacco translates into quick benefits and sustained over time: there is a reduction of coronary events of 50% per year and a reduction in mortality after an infarction of 25-50%.

After up to 15 years the risk of having a stroke is around the same as someone who has never smoked (5,17).

High blood pressure: the relationship between arterial pressure (PA) and the risk of cardiovascular events is practically linear, and there is no point below which there is no risk. The general objective for all people, including patients who have already had a cardiovascular event, is a PA <140/90 mmHg (18).

Dyslipidaemia: The higher the levels of LDL-C, the greater the risk of suffering a cardiovascular event. And on the contrary, by decreasing LDL levels (especially with statins), a significant reduction in cardiovascular events is observed. This has been reflected in clinical practice guidelines, with decreasing LDL targets after a cardiovascular event. Simultaneously, high HDL levels are associated with cardiovascular protection (5,19).

Diabetes: The damaging effect that diabetes has on the arteries is closely related to the duration of diabetes, poor glycaemic control and the association with other risk factors for cardiovascular disease, such as AHT. Atherosclerosis in diabetic patients forms earlier, is more extensive and more often affects small arteries and therefore has less chance of revascularization (20).

Sedentary lifestyle: A sedentary lifestyle and the loss of strength and muscle mass, is associated with a higher rate of obesity, high blood pressure, and less control over diabetes and cholesterol levels. Thus, it has atherogenic effects in the vasculature (19,21).

Obesity: Obesity and increased adipose tissue influence the pathogenesis of atherosclerotic inflammation process. Furthermore, obesity leads to insulin resistance and endothelial dysfunction (5,22).

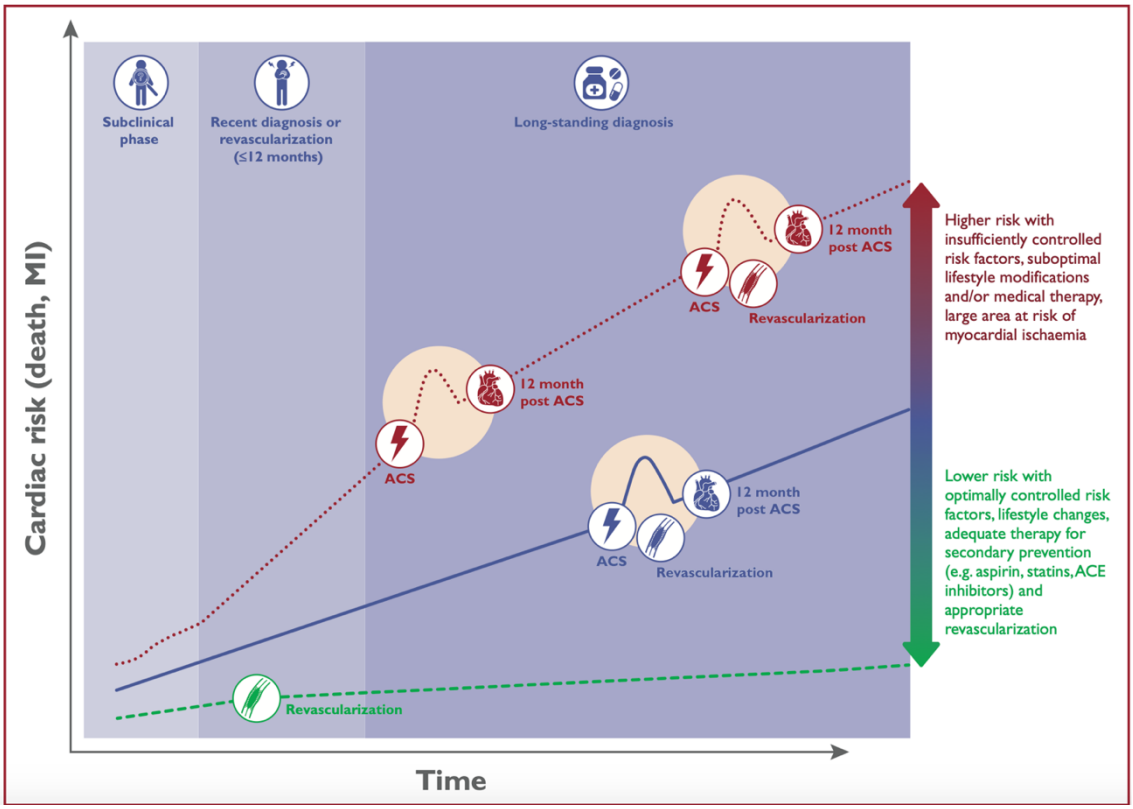

Figure 2. Schematic illustration of the natural history of chronic coronary syndromes. Extracted from (23).

1.2 CHRONIC CORONARY ARTERY DISEASE: STABLE ANGINA

1.2.1 CLINICAL FEATURES

There may be different clinical scenarios in chronic CAD suspected or established.

Most people with early coronary heart disease (less than 50 percent of stenosis) experience no symptoms. However, as atherosclerosis progresses, especially if left untreated, symptoms can appear (5).

The classic clinical feature of angina is a precordial pain of oppressive characteristics, with or without radiation on top of the arms (mainly the left arm), the neck, the jaw, the middle of the abdomen or the shoulders. The classification of the severity of angina is explained in Annex 1.

Stable angina symptoms usually follow activities that increase myocardial demand and these symptoms resolve with rest in 1 to 5 minutes.

The average frequency of angina attacks is about two per week (24).

1.2.2 DIAGNOSIS

Patients who present with acute angina should undergo a complete physical examination and a meticulous history which should always involve obtaining information about the nature, location and duration of the pain and the activities that cause or relieve it, to determine the probability of CAD before undergoing additional testing and to classify angina as stable or unstable (24).

There are two types of tests mainly for diagnostic evaluation of patients with clinical features suggestive of stable CAD:

- Anatomical: CT scan, cardiac MRI and coronary angiography (catheterization). They allow study of the coronary arteries, but do not report the hemodynamic impact of the lesions.

- Functional: conventional ergometry, isotopic ergometry (SPECT) and stress echocardiography. They detect ischemia caused by coronary lesions, but do not allow an assessment of the anatomy.

They consist of causing ischemia and detecting it:

To provoke it, physical exercise or drugs (dobutamine, dipyridamole) can be used.

To detect it, the ECG (low sensitivity and specificity, due to the fact that segmental alterations occur earlier than electrocardiographic), stress echocardiography or isotopic scintigraphy (more sensitive and specific than the stress test) can be used.

In general, whenever possible, a screening test for imaging associated ischemia is recommended, avoiding ergometry or conventional stress test (25–27).

1.2.3 MANAGEMENT

Modification of lifestyle habits, control of modifiable cardiovascular risk factors (diabetes, dyslipidaemia, smoking, hypertension, obesity and sedentary lifestyle) and medical treatment are the apex of the therapeutic management of stable ischemic heart disease. All patients with ischemic heart disease should receive an annual influenza vaccine for cardiovascular prevention (5,28,29).

- Medical treatment:

The objectives of pharmacological management of CAD patients are to reduce angina symptoms and exercise-induced ischemia, and to prevent cardiovascular events.

Then, there are two drugs that have been shown to increase the survival of this type of patient and unless there is a contraindication, they should be prescribed in all patients with ischemic heart disease:

- Low-dose acetylsalicylic acid (ASA): aspirin therapy doses of 75 mg to 325 mg daily are associated with the best risk–benefit ratio (30).
- High potency statin: the beneficial effect of statins on endothelial function is due to their anti-inflammatory and antioxidant properties, in addition to reducing LDL-c levels (8).

In addition, there are drugs for the symptomatic treatment of angina, although they do not prolong survival. These drugs restore the balance between oxygen supply and demand in the myocardium, through different mechanisms.

The 3 traditional classes of anti-ischemic drugs commonly used in the management of angina are (27,30,31):

- Non-dihydropyridine calcium antagonists (verapamil and diltiazem): they reduce myocardial oxygen demand at rest and during exercise by slowing heart rate and contractile responses. However, they also increase coronary blood flow, mainly to the epicardial regions supplied by severely narrow coronary arteries.

- Beta-blockers: they attenuate heart rate, systolic blood pressure and contractile responses at rest and during exercise.
- Nitrates: they improve exercise tolerance and produce systemic vasodilation that reduces left ventricular systolic wall stress.
- Dihydropyridine calcium antagonists (amlodipine, nifedipine): They act selectively in the arterial endothelium producing vasodilation, therefore increasing the supply of O2 to the myocardium. This type of calcium channel blockers can be administered simultaneously with beta-blockers (unlike verapamil and diltiazem).

- **Revascularization:**

Within stable ischemic heart disease there may be different situations: patients with stable angina in whom the possibility of revascularization has not been evaluated, patients with non-revascularizable chronic angina and asymptomatic patients with known ischemic heart disease (after surgery, PCI or after an ACS).

The objective of revascularization is to improve the prognosis or the symptoms and quality of life of patients with CAD. It comprises 2 aspects: the indication and selection of the type of revascularization and the performance of the intervention.

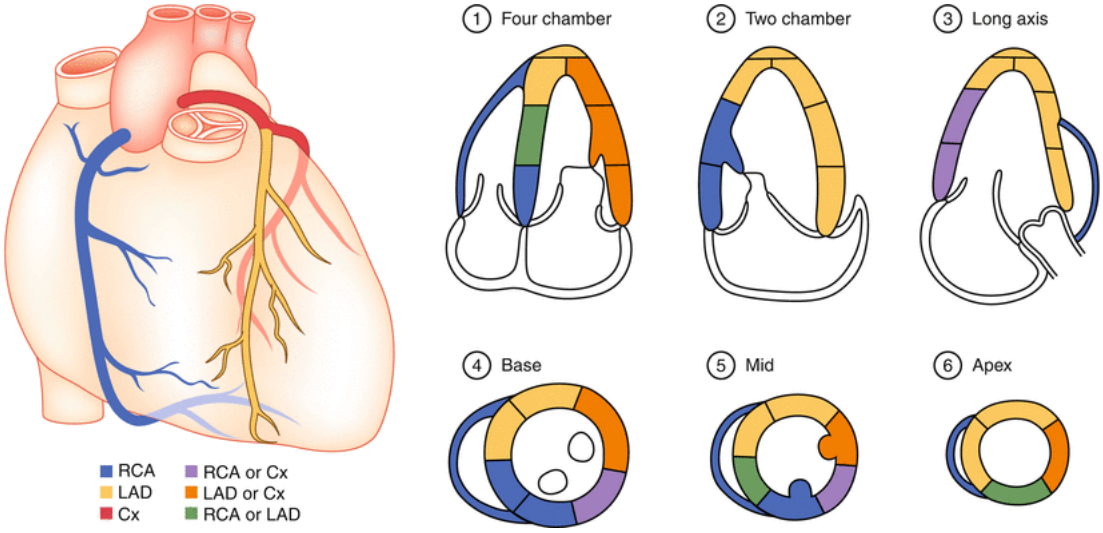

Figure 3. Typical distributions of the RCA, the LAD and the Cx coronary arteries. The arterial distribution varies between patients. Some segments have variable coronary perfusion. Extracted from (32).

The indications for revascularization in patients with stable CAD who receive medical treatment recommended by the guidelines, are persistence of symptoms despite medical treatment (refractory angina) and/or improved prognosis (severe coronary disease or large areas of ischemia). Simultaneously, the need for revascularization due to symptoms has a subjective aspect depending on the perception of their severity according to the Canadian Cardiovascular Society classification (33–35).

Following, the revascularization process can be performed in two ways, depending on the type of coronary involvement:

- Percutaneous Coronary Intervention (PCI): the catheter is inserted through the radial artery for stent implantation. In general, indicated in lesions of one or two vessels (29).

- Coronary artery bypass grafting (CABG): when the disease affects the left coronary artery or the three main vessels, especially in diabetic patients, surgical revascularization is the choice. In this option, the internal mammary artery is used whenever possible (greater durability) or a large saphenous vein is extracted from one leg (36).

1.3 THE ROLE OF STRESS ECHOCARDIOGRAPHY IN STABLE ANGINA

Stress echocardiography is the combination of 2D echocardiography with a physical or pharmacological stress, this fact increases the precision to detect myocardial ischemia. Therefore, is a highly useful technique to assess the extent and severity of CAD, whether suspected or known. The stress echocardiogram is used routinely for the diagnosis of CAD in patients with angina. Nevertheless, an equally important objective in the non-invasive evaluation of stress studies is to identify patients at risk of future cardiac events and evaluate the prognosis, with the objective that patients identified as high risk of adverse events may be intervened early to alter the natural history of the disease, and thus improve its prognosis (2).

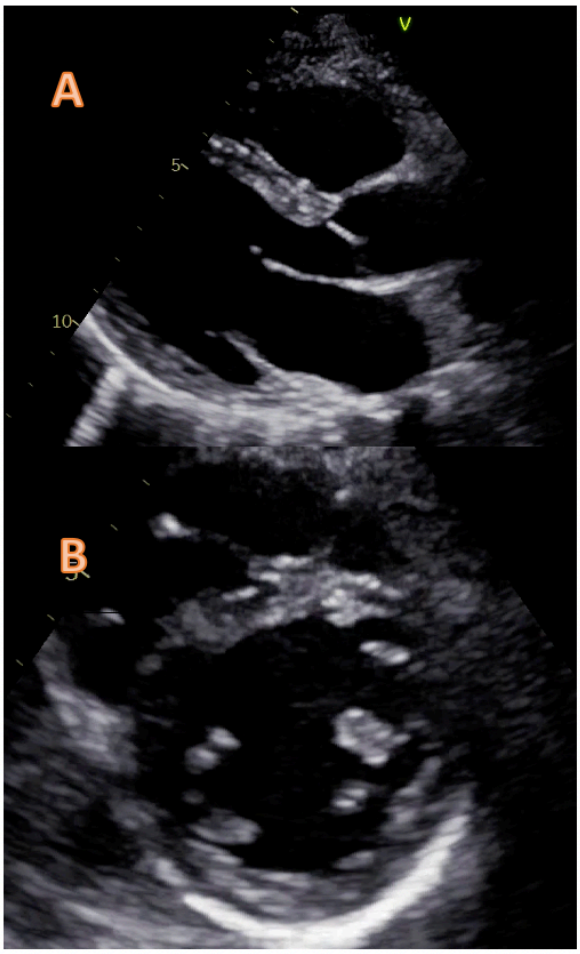

Figure 4. Long-parasternal (A) and short-parasternal (B) views.

The objective for the detection of myocardial ischemia is to cause a momentary decline in regional function during stress. Stress echocardiography provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging or magnetic resonance, but at a substantially lower cost and without environmental impact (37).

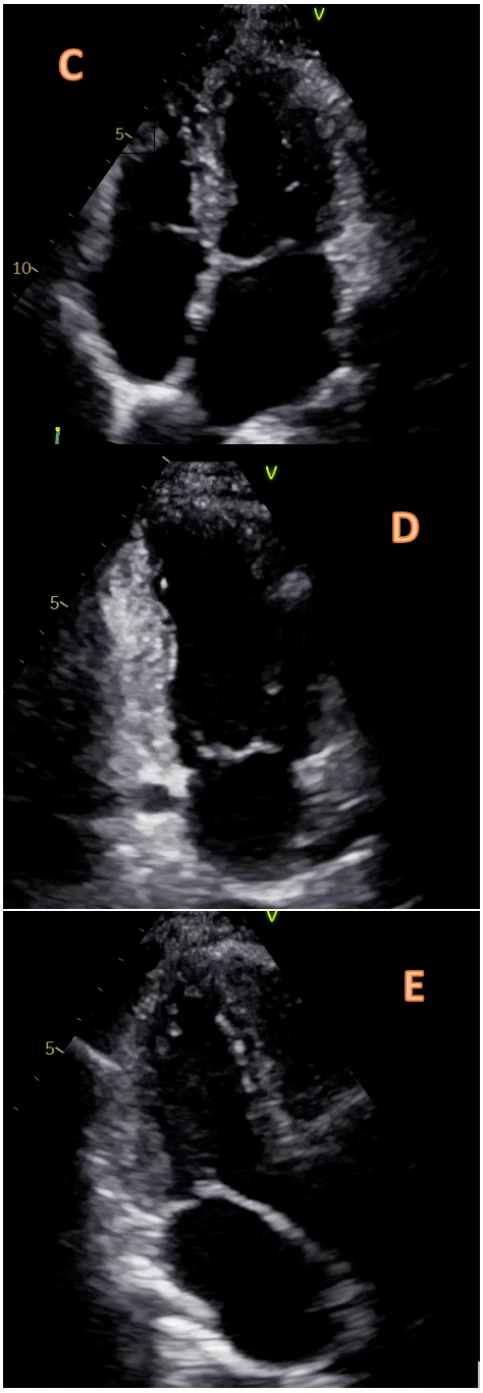

Figure 5. Apical 4 chamber (C), Apical 2 chamber (D) and Apical 3 chamber (E) views.

The three most common stressors are exercise and pharmacological (dobutamine and dipyridamole).

The exercise stress echocardiogram is the prototype of demand-driven ischemic stress and the most widely used. It is indicated in situations in which the stress test (conventional ergometry) has a limited value, also, when it can be a false negative or positive, for example in women.

The pharmacological stress echocardiogram is indicated when the patient cannot perform physical effort (recent fractures, handicapped people, lower extremity injuries, neurological compromise, etc.) or is contraindicated (38): dobutamine (a sympathomimetic amine (39)) is the best test for viability and dipyridamole the safest and simplest pharmacological stress and the most suitable for combined wall motion coronary flow reserve assessment.

Despite its reliance on operator training, stress echocardiography is today the best imaging option (most cost-effective and risk-effective) possible to achieve the goal of non-invasive diagnosis of CAD, with a sensitivity of 78-82% and specificity of 82-86% (2,37,40).

1.3.1 PATHOPHYSIOLOGICAL MECHANISMS

The mechanism is based on inducing stress ischemia to unequal coronary flow and myocardial oxygen demand, the signs and symptoms of which can be used as a diagnostic tool and which can be detected by visualizing segmental alterations in left ventricular motility on echocardiography.

Simultaneously, myocardial ischemia produces a typical cascade of events that can be classified hierarchically in a well-defined time sequence.

Flow heterogeneity (between subendocardial and subepicardial perfusion) is the precursor of ischemia, followed by metabolic changes, alteration of regional mechanical function, and only at a later stage do electrocardiographic changes and pain appear.

Regardless of the stress used, ischemia tends to propagate centrifugally with respect to the ventricular cavity: it mainly affects the subendocardial layer, whereas the subepicardial layer is affected only at a later stage if the ischemia persists.

Also, the normal response of the myocardium to exercise or pharmacological stress can be seen on echocardiography as an increase in the thickness of the walls.

Therefore, a comparison at rest and under stress, of different acquired views, allows detecting the differentiations of the segmental motility of the left ventricle (37,41–43).

1.3.2 DIPYRIDAMOLE EFFECT

Dipyridamole is a vasodilator that inhibits endogenous adenosine cellular reuptake, which produces coronary vasodilation by opening the potassium channels, thus increasing its extracellular availability to bind to receptors and, therefore, ends up producing vascular smooth muscle relaxation.

Moreover, dipyridamole inhibits thrombus formation when administered chronically.

The regions of the myocardium supplied by normal arteries experience increased blood flow due to vasodilatation. But the myocardium supplied by stenosed vessels may have only a minimal reserve capacity to dilate and therefore will not be able to increase blood flow at the same rate as in more normal territories. True coronary steal can occur if the area distal to the severe stenosis is dependent on collateral flow for the supply of normal resting blood flow. With dipyridamole, collateral flow can be significantly reduced, resulting in an absolute decrease in blood flow and consequent acute myocardial ischemia.

Intravenous dipyridamole produces maximum coronary vasodilation 5 minutes after administration and its effects persist for 10 to 30 minutes. An injection of aminophylline, a competitive non-selective antagonist of endogenous adenosine, rapidly reverses the effects of dipyridamole.

Overall, with dipyridamole, heart rate increases 20% to 40%. Systolic blood pressure and diastolic blood pressure drop slight.

The most frequent adverse effects of dipyridamole are (in descending order) hypotension, headache, dizziness or nausea.

Also, elevated adenosine levels triggered by dipyridamole infusion, can provoke bronchospasm, so patients with recent respiratory failure, severe chronic obstructive pulmonary disease (COPD) or acute asthma should not undergo a dipyridamole stress test (44–46).

2. JUSTIFICATION

CAD is a very prevalent disease and patients with stable angina are at risk of developing ACS (47), which makes their early diagnosis of great importance.

One of the most important tests today to assess the prognosis and stratify the risk in chronic CAD already diagnosed and confirm suspected ischemic heart disease, is stress echocardiography. Although PCI had previously been the Gold Standard to establish the diagnosis of CAD, nowadays, a more appropriate use is made of this interventional procedure, performing it once the diagnosis of CAD has been established through non-invasive imaging tests (48).

In 2019, at the Hospital Universitari de Girona Doctor Josep Trueta, 355 exercise stress echocardiograms were performed due to suspected CAD. Nevertheless, there were 118 patients with an inconclusive test.

Our research is to address the lack of help available to this type of patient.

In order to solve this issue, it is proposed that, in patients who have obtained an uncertain result in the exercise stress echocardiography, the same test is applied consecutively by adding dipyridamole, in order to ensure maximum diagnostic performance.

However, the most physiological way to produce myocardial ischemia is exercise, then, in patients who obtain a conclusive result with only-exercise test, they would not benefit from injecting dipyridamole, so the intention is not to substitute one test for the other.

It would be very interesting to find a way to sensitize stress echocardiography for patients who have an inconsistent test, taking advantage of the benefit of an imaging test, with no environmental impact, no biological effects for both patient and operator and lower cost, compared to equally accurate but less sustainable competing techniques.

Furthermore, we believe that certain characteristics of the patient may make the dipyridamole test more sensitive to detect ischemic heart disease, especially all those

variables related to cardiovascular risk factors, since the higher the risk, the more likely that chest pain is of coronary origin.

It would be inherently useful, in addition, to avoid both the restlessness of being without diagnosis, on an emotional level, as well as the physical risks, as the progression of the disease with its intrinsic complications that can even lead to death, without adequate treatment.

Moreover, this is a very innovative topic because, although the dipyridamole-exercise stress test is used in nuclear medicine to perform myocardial SPECT, at the moment, there are no studies evaluating the effect of dipyridamole together with exercise in stress echocardiography.

3. HYPOTHESIS

Our hypothesis is that dipyridamole infusion to exercise stress echocardiography allows the identification of a significant proportion of patients with CAD, with an inconclusive result in a prior exercise stress echocardiography.

4. OBJECTIVES

4.1. PRIMARY OBJECTIVE

The main objective of this study is to verify whether dipyridamole infusion to exercise stress echocardiography allows the identification of a significant proportion of patients with CAD, with an inconclusive result in a prior exercise stress echocardiography.

4.2 SECONDARY OBJECTIVE

- To assess what adverse effects appear dipyridamole combined with exercise.

- To analyse what characteristics of the patient can make dipyridamole more useful in identifying ischemic heart disease.

5. STUDY

5.1 MATERIAL AND METHODS

5.1.1 STUDY DESIGN

This is a descriptive cross-sectional study and description of the diagnostic test.

5.1.2 STUDY POPULATION

In our study we will include patients with suspected ischemic heart disease who have inconclusive exercise stress echocardiography in Hospital Universitari de Girona Doctor Josep Trueta, and who meet the inclusion criteria.

5.1.2.1 INCLUSION CRITERIA

- Patients who, having suspected chest pain of coronary origin, undergo an exercise stress echocardiography that is inconclusive, considered when the patient does not reach 85% of the theoretical age-adjusted maximum heart rate.
- Men or women at least 18 years old.
- Patients who have read, understood and voluntarily signed the informed consent before participating in the study.

5.1.2.2 EXCLUSION CRITERIA

- Decompensated bronchial asthma or COPD
- Severe hypotension
- Second degree AV block
- Hypersensitivity to dipyridamole
- Very poor acoustic window

5.1.3 SAMPLE

5.1.3.1 SAMPLE SELECTION

The selection will be made with a consecutive, non-probabilistic sampling method of the patients who have come to the Hospital Universitari de Girona Doctor Josep Trueta to perform an exercise stress echocardiography, due to suspected CAD and the test has not been consistent. The patients attending the study will be selected when the non-conclusive stress echocardiography has finished.

5.1.3.2 SAMPLE SIZE

Calculation of the sample size has been done using GRANMO application version 7.12.

A sample size of 77 subjects randomly selected will suffice to estimate with a 95% confidence and a precision +/- 5 percent units, a population percentage considered to be around 95%. It has been anticipated a replacement rate of 5%.

In Hospital Universitari de Girona Doctor Josep Trueta, every year there are at least 100 patients with inconclusive results in the test, therefore the time needed for collecting all the data necessary for our study will be approximately of 1 year.

5.1.4 VARIABLES

Since this is a cross-sectional study, independent and dependent variables cannot be identified.

5.1.4.1 MAIN VARIABLE AND MEASURE INSTRUMENTS

- **Proportion of patients with the presence of ischemia observed on dipyridamole-exercise echocardiography test:**

This is our variable of interest or outcome variable.

Ischemia is observed with reduction in ventricular motility (hypokinesia/akinesia) during stress, that was not present at baseline or was less severe.

The movement of a ventricular segment is influenced by the movement of the adjacent segments, therefore, the study of mobility will be combined with the evaluation of the thickness in systole to define the presence of a regional anomaly.

Based on the results obtained, patients will be classified according to whether they obtain a positive test (ischemia) or not, which will remain inconclusive.

To obtain this variable, the dipyridamole-exercise echocardiography test (protocol attached in annex 5) will be performed, with the following measurement methods to diagnose ischemia:

- Obvious electrocardiographic positivity (ST segment with decrease/increase ≥ 1 mm at 80 milliseconds from the J point with respect to the baseline).
- Clinically positive: suggestive symptoms of angina.
- Obvious echocardiographic positivity (with hypokinesia/akinesis of ≥ 2 LV segments): the interpretation of the images will be carried out following the *17-Segment Left ventricle Model* recommended by AHA (annex 7) and each segment will be assigned the following score based on movement and thickening (normal = 1, hypokinesia = 2, akinesia = 3 and dyskinesia = 4).

    - **Normal:** movement and thickening of the wall increase with exercise.
    - **Hypokinesia:** reduced thickening (less than 5 mm).
    - **Akinesia:** no thickening.
    - **Dyskinesia:** there is no thickening and the movement is outward.

REST	+	STRESS	=	DIAGNOSIS
Normokinesis	+	Normo-hyperkinesis	=	Normal
Normokinesis	+	Hypo-, A-, Dyskinesia	=	Ischemia
A-, Dyskinesia	+	A-, Dyskinesia	=	Necrosis

Table 1. Echocardiographic diagnosis according to findings.

5.1.4.2 COVARIATES

These covariates can be used to find out if there are certain patient characteristics that increase the sensitivity of the dipyridamole-exercise stress echocardiography test to detect ischemic heart disease. All of these covariates will be collected by reviewing the medical history or during the anamnesis.

- Gender: dichotomous qualitative variable (male/female). It has been expressed as an absolute value and a percentage.

- Age: discrete quantitative variable. It will be defined in years. Age is important since it is correlated with a higher probability of cardiac events. It has been expressed as an arithmetic mean and standard deviation.

- Type of chest pain: dichotomous qualitative variable (typical/atypical pain). The patients will be given the questionnaire for stable angina devised by Rose and Blackburn and adopted by the WHO (Annex 6).

- Hypertension: Yes/No, according to the Spanish clinical guidelines of AHT.

- Diabetes mellitus: Yes/No, according to Spanish clinical guidelines for DM.

- Dyslipidaemia: Yes/No, according to the Spanish clinical guidelines for Dyslipidaemia.

- Peripheral arterial disease: Yes/No. If there is clinical intermittent claudication and/or diagnostic tests of peripheral vascular disease.

- Personal or family history of CAD: Yes/No.

- Current smoker: Yes/No. Defined according to the WHO definition of smoking. It will be taken into account that the patient is a non-smoker after one year without smoking.

- Left ventricular ejection fraction (LVEF): categorical qualitative variable (preserved> 50%, mild 40-50%, moderate 30-39.99% or severe dysfunction <30%). It will be expressed as an absolute value and a percentage (collected on previous echocardiography performed).

5.1.5. STATISTICAL ANALYSIS

Our study will include three levels of statistical analysis of the data collected: univariate analysis, bivariate analysis and multivariate analysis. The calculations will be made using the SPSS statistical package version 26.0.

Descriptive univariate analysis

First, to describe the characteristics of the study population, if the variable is continuous, it will be described with the mean and its standard deviation (if a normal distribution can be assumed) or median, first or third quartile (if a normal distribution cannot be assumed). If the variable is categorical, it will be done with a proportion and its 95% confidence interval.

Bivariate analysis

It will be the comparison between the characteristics of the patients that we have been able to identify with dipyridamole test, compared to those who have not been able to classify, in this bivariate analysis, if the variable is continuous, we will use a student's T test and for categorical variables, a Chi square test will be used. If there is any nonparametric variable and we have to compare means, we will use the Mann-Whitney U test.

Multivariate analysis

To determine which variables are associated with identifying or not CAD, a logistic regression model will be made, where we will put all these candidate variables to see if they are associated with identifying the disease.

We will assume a confidence interval of 95% and P value <0,05 to consider that there is a significance difference.

5.2 ETHICAL AND LEGAL CONSIDERATIONS

In the first instance, before carrying out the study, the research protocol must be sent to the Comitè d'Ètica d'Investigació Clínica (CEIC) of the Hospital Universitari Doctor Josep Trueta. Any recommendation from the committee to improve the procedure will be considered.

This study will be carried out accomplishing and scrupulously respecting the following principles and regulations:

- The "Ethical Principles for Medical Research Involving Human Subjects"(49) stated by the World Medical Association in the *Declaration of Helsinki* (reviewed in 2013), guaranteeing ethical principles and human rights.

- The "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"(50). Therefore, all participants who meet the inclusion criteria will be duly informed through an information sheet (Annex 2) about the infusion procedure of dipyridamole in echocardiography and the study before being included. As previously mentioned, it is an inclusion criterion that the subjects have voluntarily signed the informed consent (Annex 3) in order to participate in the study.

- The "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"(51). To ensure and protect the confidentiality of all participants, as well as their personal data. Then, to maintain confidentiality, patient information will only be used for the purpose of research and will always be analysed anonymously.
- The "Ley 29/2006 de 26 Julio, de garantías y uso racional de los medicamentos y productos sanitarios" (52).

The research team will declare that they have no conflicts of interest, and that they do not receive any financial compensation for collaborating in the study, on the contrary, they will declare an absolutely altruistic purpose for the benefit of human health and medical advance. Simultaneously, the researchers of this project will ensure that all results will be published with transparency and clarity, avoiding any unfavourable exclusion of data.

5.3 LIMITATIONS

In our research protocol, there are several limitations that need to be considered because they may interfere with our study.

- First of all, we are aware that this is not a common comparative study between a diagnostic technique and the Gold Standard (GS). Currently we have no other test that can act as a Gold standard because its benefits have been shown to be better to confirm ischemic heart disease, in this level of suspicion. Therefore, this is the main limitation of this study, not having a gold standard to compare our test with. In such a way that we will simply dedicate ourselves to describing the results of applying a diagnostic test, the proportion of patients that we can diagnose using stress echocardiography with dipyridamole, within which they have been classified as inconclusive.

- Another important limitation is that with a descriptive cross-sectional study, as is the case with this design, we cannot establish causal inferences; thus, we can only speak of an association between our variables.

- It must be taken into account that, having used a non-probabilistic consecutive sampling method for the selection of the sample, the selection bias could be present.

- Also, some covariates have been taken into account to avoid confounding bias in the statistical analysis, but we are aware that it is not possible to take them all into account.

- Echocardiography is an operator-dependent test, because of this, we will try to minimize it by standardizing the parameters of the test, making a consensus meeting of the technique between all the researchers who will do it and the collected images will be interpreted by 2 cardiologists who are experts in cardiac imaging.

- Finally, since there will be different people who will be collecting the data, there could be a bias in the data collection process, to minimize this risk, just as a meeting will be held to agree on echocardiographic techniques, we will have a meeting with all the investigators involved in the study to explain the exact process and ensure that everyone fills out the case report form in the same way.

5.4 PROJECT IMPACT AND APPLICABILITY

In this technological revolution, non-invasive images play a fundamental role, not only in the diagnosis of CAD, but also in assessing the choice of the appropriate treatment, establishing the prognosis, and all this at a lower cost and with a much lower risk than performing a percutaneous intervention.

Simultaneously, in this population of patients who do not have a diagnosis, taking into account that chest pain could be of non-coronary origin, the risks outweigh the possible benefits and, therefore, are patients for whom catheterization would not be indicated and it would be unethical to do so. Even so, it is not a good solution to stop labelling the aetiology, since some of these patients will have chest pain of coronary origin and leaving them without a diagnosis entails, on the one hand, uncertainty in the clinical management, and on the other hand, a high risk of progression of CAD with the consequent risk of MI.

In addition, this study is clinically relevant, firstly, because thus far, no data are available on dipyridamole in exercise stress echocardiography and, secondly, because if the results are positive, patients with suspected CAD who have an inconclusive test, may benefit from a diagnosis, thus avoiding treatment delay, disease progression and consequent complications what this entails.

5.5 WORK PLAN

The entire study process is expected to last 1 year and a half. The activities carried out during this time will be organized in the following 4 phases. Chronogram is attached in annex 4.

PHASE 1: PREPARATION AND COORDINATION

This first part of the study lasts three months and consists of the development of the current protocol from September until the beginning of December 2020.

To specify the tasks that all team members will be in charge of, researchers, collaborators, and statisticians will meet. Data collection methods will be discussed and established, and the schedule will be corrected with the collaboration of the members of the research team. Also, during this first part, we will give a consensus assembly for the echocardiography parameters, with all the researchers participating in the data collection process to ensure that it is done in a standard way. Once the protocol is ready and approved by the entire participating team, we will present it to the Comitè d'ètica de l'Hospital Universitari de Girona Doctor Josep Trueta, for evaluation and approval.

In order to control the data collected, evaluate the progress of the study, identify deficiencies and correct methodological flaws, the researchers will meet once.

PHASE 2: DATA COLLECTION

This part of the study lasts 1 year (from December 2020 until December 2021) and consists of the recruitment of patients with the inclusion/exclusion criteria described above and data collection. As we collect patients who meet the inclusion criteria, they will be summoned a week later to perform the dipyridamole-exercise stress echocardiography test (Annex 5).

We hope to reach the required sample size of 77 patients during this phase.

PHASE 3: STATISTICAL ANALYSIS PROCESS

A statistician will participate in the study so that the statistical analysis is carried out with guarantees of excellence. This part of the study should last 1 month (from January to February 2022).

A meeting will be held with the research team to extract and evaluate the preliminary conclusions and results.

PHASE 4: PUBLICATION AND DISSEMINATION

During the last two months, the researchers will write and edit a scientific paper to publish. The results will be presented in a number of congresses, including:

- Congreso de la sección de imagen cardíaca de la Sociedad Española de Cardiología (SEC).
- Congrés de la Societat Catalana de Cardiologia (SCC).

5.6 BUDGET

The activities necessary for the study only consist of a stress echocardiogram with dipyridamole infusion, the price is 195€, which already includes the nursing task and the corresponding cardiologist specializing in cardiac imaging.

Since the means in terms of personnel and material are already available, once the study has been accepted by the ethics committee and the budget approved, it can be carried out in compliance with all the aspects involved in this protocol.

EXPENSES	COSTS
1.Personal expenses	
2.Executive expenses	
Consensus meeting echocardiography	0 €
Statistical Analysis (x90h, per 35€/h)	3.150 €
Stress echocardiography + Dipyridamole infusion (195€x77)	15.015 €
Office consumables and others	100 €
3.Publications and dissemination expenses	
Scientific publications	1.500 €
Attendance to scientific meetings and congresses (SCC and SEC).	1500x2=3000€
TOTAL	22.765 €

Table 2. SCC: "Societat Catalana de Cardiologia"/SEC: "Sociedad Española de Cardiología"

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ANNEX 1: CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION OF ANGINA

GRADE	DESCRIPTION
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or 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 a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

ANNEX 2: INFORMATION SHEET FOR THE PATIENT

FULL D'INFORMACIÓ A PARTICIPANTS

CODI DEL PROJECTE: _____

1. **Generalitats del projecte:** El present estudi observacional serà dut a terme per la unitat d'Imatge cardíaca de l'Hospital Universitari de Girona Doctor Josep Trueta, en els pacients amb sospita de cardiopatia isquèmica i una ecocardiografia d'estrés amb exercici no concloent. El projecte de recerca ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital.
2. **Objectius i finalitats de l'estudi:** La finalitat d'aquest estudi és avaluar la viabilitat d'utilitzar l'ecocardiografia d'exercici durant la vasodilatació amb dipiridamol, amb la finalitat de detectar cardiopatia isquèmica, en pacients on l'ecocardiografia amb només exercici no és concloent.
3. **Participació:** La seva participació en l'estudi és totalment voluntària i no s'obtindrà cap compensació econòmica. La tasca del participant, es basa en repetir-se la prova d'ecocardiografia d'estrés amb exercici i infusió de dipiridamol.
4. **Riscos:** També recordem els possibles efectes adversos del dipiridamol: hipotensió, mal de cap, marejos o nàusees. S'ha de tenir en compte que el dipiridamol s'utilitza actualment amb molta freqüència en processos diagnòstics i això està estrictament controlat. Tot i així, al final del protocol de la prova s'injecta aminofilina, que reverteix ràpidament l'efecte del dipiridamol.
5. **Confidencialitat i protecció de dades:** S'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la Llei Orgànica 3/2018 i les dades recollides seran gestionades de forma anònima i només utilitzades amb fins d'investigació.
6. **Resultats i beneficis de la investigació:** El pacient està en el seu dret de ser informat dels resultats de la investigació. Els beneficis derivats de la investigació, tan poden beneficiar al participant com a altres persones, i aquests seran adequadament utilitzats per assolir els objectius de l'estudi i serviran de base per a futures investigacions en aquest àmbit.

Gràcies per la seva participació.

ANNEX 3: INFORMED CONSENT

Declaració del participant:
Jo,_____, amb DNI _____ certifico que:

- - He llegit detingudament el full informatiu sobre l'estudi.
- - He tingut oportunitat de fer totes les preguntes necessàries respecte l'estudi.
- - Estic satisfet en relació a la quantitat d'informació rebuda.
- - He estat informat por l'investigador _____ sobre les implicacions i finalitats de l'estudi.
- - Entenc que la meva participació és voluntària.
- - Entenc que les meves dades i proves seran etiquetades amb un codi numèric a fi de mantenir la confidencialitat.
- - Entenc que puc, conforme la "Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica", revocar el consentiment de participació a l'estudi, sense tenir que justificar-ho, i sense que això afecti a la meva assistència sanitària.

Accepto que els investigadors principals del projecte puguin contactar-me en el futur si es considera oportú:

☐Sí ☐No

Lliurement dono la meva conformitat per participar a l'estudi aportant dades de la meva història clínica:

☐Sí ☐No

Autoritzo que futurs estudis similars a aquest, utilitzin les dades de la meva història clínica, com a font de dades epidemiològiques:

☐Sí ☐No

Signatura del participant Signatura de l'investigador

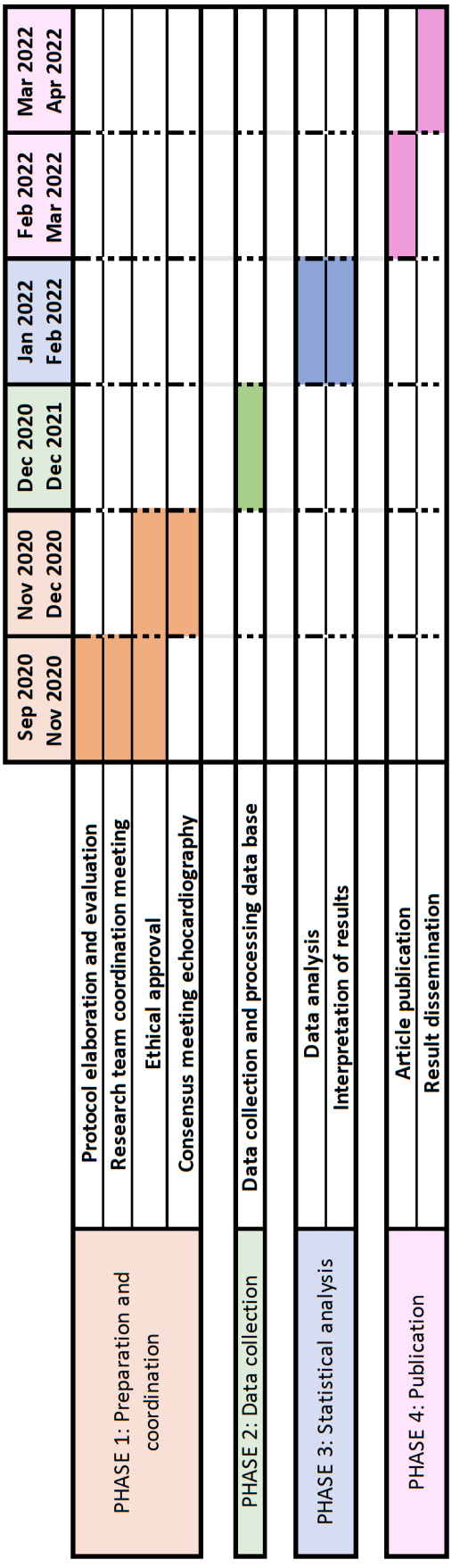
Data: __/__/____ Data: __/__/____

REVOCACIÓ DEL CONSENTIMENT

Jo,_____, amb DNI _____revoco el consentiment de participació a l'estudi.

Data: __/__/____ Signatura

ANNEX 4: CHRONOGRAM



ANNEX 5: DIPYRIDAMOLE-EXERCISE ECHOCARDIOGRAPHY TEST PROTOCOL

DIPYRIDAMOLE-EXERCISE STRESS ECHOCARDIOGRAPHIC TEST PROTOCOL

Due to the incorporation of this protocol, all patients will be instructed to fast for at least two hours before the test and to abstain from b-blockers, caffeine and other xanthines for a minimum of 24 hours beforehand.

For the dipyridamole infusion the same protocol will be used as in the SPECT dipyridamole stress test, used in the Hospital Universitari de Girona Doctor Josep Trueta, but applied to echocardiography.

Stress echocardiography will be performed using a GE (General Electric) supine bicycle connected to computer with cardiosoft software for continuous ECG analysis, a GE Vivid E95 ultrasound with 3D matrix probe and software package 3.0.

Images will be digitally captured and analized with GE Healthcare's cardiology echoPAC software 3.0.

During the stress echo, the electrocardiographic leads are placed following the protocol of a conventional stress test. A 12-lead ECG is recorded at rest and every minute during the exam. Three ECG lead is also continuously displayed on the echo monitor to provide the operator with a reference for ST segment changes and arrhythmias.

The blood pressure is measured at rest and at each stage thereafter.

Images are recorded first at rest, before exercise. At least this four echocardiographic views or windows will be taken: long-parasternal, short-parasternal, apical 4 chamber, apical 2 chamber and apical 3 chamber.

The patient pedals against an increasing workload at a constant cadence (usually between 55-65 rpm).

When the patient is making the maximum effort and anticipating that he will endure two more minutes, 0.56 mg/kg of dipyridamole is administered intravenously for 1 minute and while maintaining physical effort, once it has been injected and until

exercise stops, the patient should hold on pedaling 1 minute more, when the images will be taken, assuming that it is the maximum peak of effort.

If the patient is not able to continue exercising at the maximum effort achieved, the load will be decreased during the dipyridamole infusion, to allow patients to maintain some level of exercise until the end of the test.

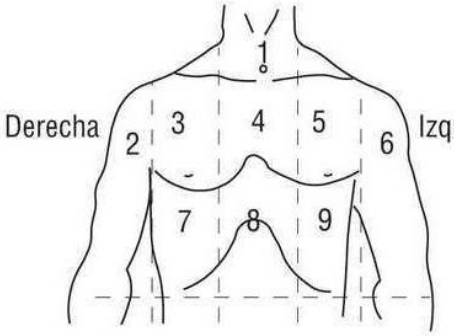
Images are taken and recorded again in the planes mentioned previously, during the recovery phase, after the cessation of stress and when 100 mg of aminophylline will be administered IV.

When all the plans have been taken, a quad screen format is used for comparative analysis.

ANNEX 6: CHEST PAIN QUESTIONNAIRE

1. ¿A veces tiene algún dolor o molestia en el pecho? Sí/No

2. ¿En qué lugar localiza este dolor o molestia?



– Esternón: – superior (1); – medio (4); – inferior (8)
– Tórax anterior izquierdo (5)
– El brazo izquierdo (6)
– Resto

3. ¿Lo siente también en algún otro sitio? Sí/No

4. Cuando camina a paso normal en llano, ¿esto le produce molestias? Sí/No

5. Cuando camina cuesta arriba o a paso rápido, ¿esto le produce molestias? Sí/No

6. Cuando caminando tiene algún dolor o molestia en su pecho, ¿qué hace?

– Para
– Disminuye la marcha
– Continúa al mismo paso

7. ¿Desaparece el dolor o la molestia en el pecho si se queda quieto? Sí/No

8. ¿En cuánto tiempo desaparece?

– 10 minutos o menos
– Más de 10 minutos

9. ¿Ha visto a un médico a causa de este dolor? Sí/No

10. En caso afirmativo, ¿qué dijo que era?

Clasificaciones del dolor torácico

– Ausencia de dolor torácico: p1) no

– Dolor torácico no de ejercicio: p1) sí; p3) y p4) no

– Angina de pecho definitiva: p1) sí; p3) o p4) sí; p2) sitios 4, 5 u 8; p5) para o disminuye la marcha; p6) sí; p7) 10 minutos o menos

– Angina de pecho grado I: p1) sí; p3) no; p4) sí

– Angina de pecho grado II: p1) sí; p3) sí; p4) sí

– Angina de pecho posible: p1) sí; p3) o p4) sí; no respuesta o no se cumple al menos uno de los cuatro criterios adicionales

ANNEX 7: 17-SEGMENT LEFT VENTRICLE MODEL