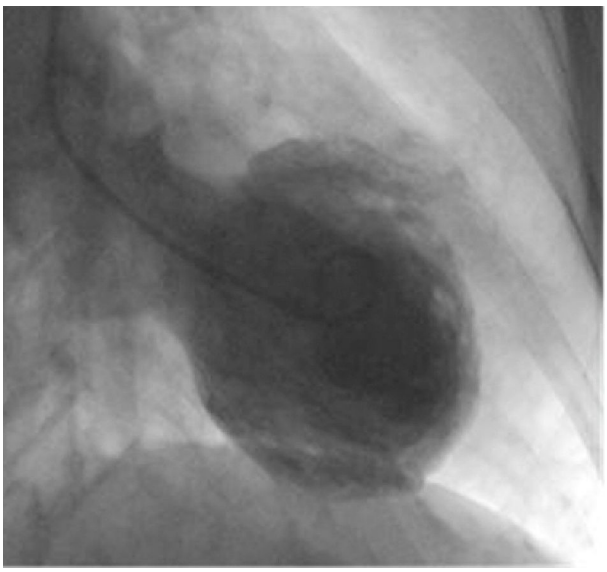
Universitat de Girona



Relationship between iodine 123 – metaiodobenzylguanidine pattern in the acute phase of Takotsubo syndrome and prognosis.

A prospective cohort study

End-of-term project

February 2018

Author: Sandra Zambrano Gómez

Tutor: Dr. Albert Bertrán

Cardiology Department

ACKNOWLEDGEMENTS

Gràcies a tot l'equip de Cardiologia i de Medicina Nuclear de l'Hospital Universitari Doctor Josep Trueta per dedicar-me el seu temps durant aquests mesos.

Gràcies al Dr. Albert Bertrán i al Dr. López Bermejo per la seva total disponibilitat i per resoldre tots els meus dubtes quan ho he necessitat.

Gràcies a la meva família, en especial als meus pares i la meva parella, per creure en mi quan ni tan sols jo ho feia.

"Science, my boy, is made up of mistakes, but they are mistakes which it is useful to make, because they lead little by little to the truth" Jules Verne.

INDEX

Pages

ABBREVIATIONS

ACEI: angiotensin converter enzyme inhibitor

ACS: acute coronary syndrome

AMI: acute myocardial infarction

BNP: brain natriuretic peptide

CK: creatinine kinase

CK-MB: creatinine kinase muscle-brain

CMRI: cardiac magnetic resonance imaging

CRP: c- reactive protein

EKG: electrocardiogram

G-SPECT: gated-SPECT

HF: heart failure

H/M: heart-to-mediastinum ratio

^{123}I-MIBG: iodine – 123 – metaiodobenzylguanidine

LV: left ventricle

LVEF: left ventricle ejection fraction

MACE: major adverse cardiac events

NE: norepinephrine

NT-proBNP: N-terminal pro-brain natriuretic peptide

PET: positron emission tomography

SNS: sympathetic nervous system

SPECT: simple photon emission computed tomography

^{99m}Tc-sestamibi: ^{99m}tecnecium-sestamibi

TDS: total defect score

Tn-I: troponin I

TTS: Takotsubo syndrome

WR: washout rate

ABSTRACT

Background:

Takotsubo syndrome has always been thought to be a benign disease, but recent studies showed that its complications are similar to acute myocardial infarction (AMI). Complications are estimated to be 9,9% per person/year if we take into account major adverse cardiac events, such as recurrence, AMI, death and stroke. Its pathophysiology is not well established yet, but it seems to be related to sympathetic activity disturbance that can be demonstrated using simple photon emission computed tomography (SPECT) with iodine-123-metaiodobenzilguanidin (^{123}I-MIBG). We know that there is a relationship between the pattern of sympathetic activity impairment in the acute phase and residual affection of ^{123}I-MIBG uptake after 2 years of follow-up but it has not been demonstrated if this residual affection has a clinical relevance in the prognosis of this type of patients.

Objective:

The aim of this study is to determine if there is a relationship between the ^{123}I-MIBG uptake pattern in the acute phase and prognosis, evaluated using major adverse cardiac events (MACE) (AMI, recurrence, re-admission, mortality from any cause and mortality from cardiovascular cause), after 3 years of follow-up. We are also interested in seeing if there are differences of each of the complications included in MACE between groups defined by Total Defect Score (TDS): TDS >8 or ≤8 and evaluate if the severity of the sympathetic activity impairment is also related to MACE.

Study design, setting and subjects:

This will be a prospective cohort, multi-centric study, with a consecutive method of sampling of patients attending the Coronary Unit with Takotsubo syndrome that meet inclusion criteria. Eleven hospitals from Catalonia will participate in the study.

The sample size will be 782 patients with Takotsubo syndrome that meet Mayo clinic criteria diagnosed in the Coronary Unit.

Methods:

The main variables of this study are the acute phase pattern of ^{123}I-MIBG uptake and long-term prognosis after 3 years of follow-up. This prognosis will be evaluated with the occurrence of any MACE.

The patients will be classified in two groups depending on the extension of cardiac sympathetic activity affection: *Group 1* moderate and severe affection (TDS >8) and *Group 2* normal or mild affection (TDS ≤8). These patients will be followed-up for 3 years.

The multivariate analysis will be done using COX model.

Keywords: Takotsubo; ^{123}I-MIBG; SPECT; MACE; prognosis; total defect score.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 WHAT IS TAKOTSUBO SYNDROME?

A. DEFINITION

Takotsubo syndrome (TTS) is an acute reversible myocardiopathy which is presented like an acute coronary syndrome (ACS), with elevation of biomarkers, changes in the electrocardiogram (EKG) and chest pain or other symptoms, typically after emotional or physical stress. It has a range of wall motion abnormalities (hypokinesia/akinesia in some segments and hyperkinesia in others) that extend beyond a single coronary vascular bed and without epicardial coronary occlusion. It produces systolic and diastolic transient dysfunction (1–4).

It is also called Takotsubo myocardiopathy, stressed-induced myocardiopathy, apical ballooning syndrome, ampullary-shaped syndrome and “broken heart syndrome”, but the most recent literature suggests that the best nomenclature is Takotsubo syndrome (5).

It was first described in 1990 in Japan, and its name was used because of the heart siluet, that seems the octopus’ pots of Japanese fisherman in the Hiroshima fish markets (3,5).

B. EPIDEMIOLOGY

The incidence of this syndrome is not well known, but it is estimated to be 1 - 2% of all ACS (6). It affects predominantly postmenopausal women (≈ 90%) between 58 and 75 years old (1,6). Emotional stressful trigger is more common in women while physical stressful trigger, shock or resuscitation on presentation is more common in men (5).

It is usual to find some cardiovascular risk factors in this population such as arterial hypertension (>50%), diabetes mellitus, alcohol abuse, psychiatric disorders, hyperlipidaemia and smoking (4,7).

Some studies talk about genetic predisposition/susceptibility, but it is not considered a genetic myocardiopathy (2,3,8).

C. TYPES

There are different types of TTS (4,5,9,10) depending on the trigger or the presentation:

- **Primary or secondary TTS**:
  - Primary TTS: in these patients, the trigger is usually emotional stress or an unknown trigger (idiopathic). They do not have another disease that can cause this wall motion alteration.
  - Secondary TTS: in these patients, the trigger is usually physical stress, such as surgery, sepsis, drugs or neurological disease (Table 1). They suppose the 20% of all the cases.

Table 1. Triggers for secondary Takotsubo syndrome (5)

- Endocrine: pheocromocytoma, thyrotoxicosis, syndrome of inappropriate antidiuretic hormone, Addisonian crisis, multiple endocrine neoplasia 2A, hyperglycaemic hyperosmolar state, hyponatremia, severe hypothyroidism, Addison's disease, adrenocorticotropin hormone deficiency, autoimmune poliendocrinesyndrome II.
- Neurological and neurosurgical: acute neurosurgical emergencies, acute neuromuscular crises, especially if involving acute ventilatory failure, epileptic seizure, limbic encephalitis, ischaemic stroke, posterior reversible encephalopathy syndrome.
- Respiratory: acute exacerbation of asthma or chronic obstructive pulmonary disease, acute pulmonary embolism, acute pneumothorax
- Obstetric: miscarriage, labour, emergency caesarean section
- Psychiatric: acute anxiety attack/panic disorder, attempted suicide, drug withdrawal syndrome, electroconvulsive therapy
- Gastrointestinal: acute cholecystitis, billary colic, acute pancreatitis, severe vomiting, severe diarrhoea, pseudomembranous colitis, peritonitis
- Infection: severe sepsis, babesiosis
- Cardiological: dobutamine stress echocardiography, radiofrequency arrhythmia ablation, pacemaker implantation, electrical DC cardioversion for atrial fibrillation, post-cardiac arrest including ventricular fibrillation
- Haematological: blood transfusion, thrombotic thrombocytopenic purpura
- Surgical: anaesthesia induction.
- Medication or illicit drugs: epinephrine injection, nortryptiline overdose, venlafaxine overdose, albuterol, flecanide, metoprolol withdrawal, 5-fluorouracil, duloxetine, cocaine abuse

– **Typical or atypical TTS**:
  - Typical TTS: the wall motion abnormality affects predominantly the apex and the mid ventricle and it is the most common affection (80%). There is hypokinesia/akinesia/dyskinesia of the apical and midventricular segments and hyperkinesia of the basal part.
  - Atypical TTS: it includes all the patients with affection of midventricular, basal or focal hypokinesia/akinesia and it is approximately 20% of all TTS. The affection of the right ventricle is also included in this type.

Patients with typical TTS are usually older, have higher levels of brain natriuretic peptide (BNP) and c-reactive protein (CRP), ST is more frequently elevated while in atypical is usually depressed and have lower left ventricle ejection fraction (LVEF) (Table 2).

Table 2. Differences between typical and atypical TTS (9)			
		Typical TTS	**Atypical TTS**
Age		Older	Younger
BNP		Higher	Lower
LVEF		Lower	Higher
ST segment		More frequently elevated	More frequently depressed
Neurologic/psychiatric diseases		Psychiatric diseases more frequent	Neurologic diseases more frequent
Troponin-I and creatinine kinase		Similar	Similar
CRP		Higher levels	Lower levels
Mortality and complications	**Hospital**	Similar	Similar
	Long – term*	Similar	Similar

** After confounder adjustment (left ventricle ejection fraction <45%, atrial fibrillation, neurologic disease)*

D. PATHOPHYSIOLOGY

The pathophysiology of TTS (8) is not well stablished yet, but the last literature suggests different hypothesis to explain this syndrome.

- In the acute phase of TTS there is an increase of cathecolamines that can produce a direct myocardic toxicity and coronary spasm, mainly at microvascular level, that together with an increase of cardiac workload contribute to a mismatch supply – demand followed by postischemic stunning.
- Coronary arteries have autonomic innervation and the increase of sympathetic cardiac activity can induce constriction of them in the context of endothelial dysfunction.
- The sympathetic hyperactivity is accompanied by metabolic abnormalities with mismatch flow – metabolism which is reflected in positron emission tomography (PET) with fluoro deshoxi glucose and perfusion.

The article suggests (8) that postischemic stunning is a protection system against the subsequent ischemic episodes and its aim is to preserve the energy, decreasing the contractile function and the metabolism, facilitating the recuperation of systolic function.

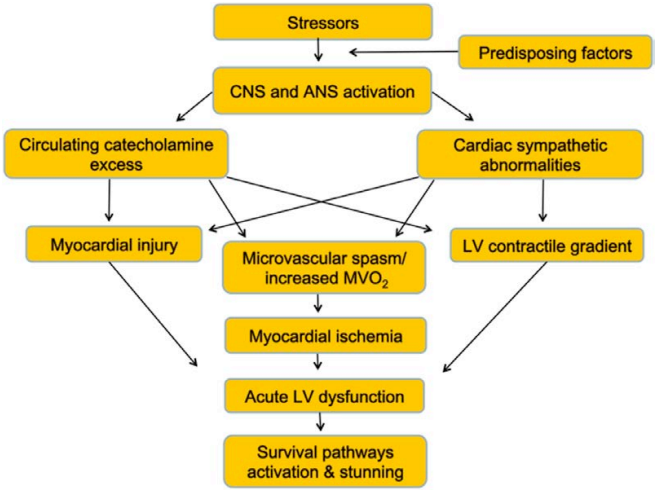


Figure 1. Pathophysiology (8)

E. DIAGNOSIS

- **Clinic:** the most common symptom is chest pain usually accompanied with vegetative symptoms. Other symptoms that are described are: dyspnoea, syncope, palpitations and cardiac arrest (4). One study found that physical stress patients are more likely to suffer from dyspnoea while emotional stress patients from chest pain (7). Other unspecific symptoms are weakness, unexplained cough and fever (8).

- **Criteria**: there are a lot of criteria to diagnose TTS, but the most used are Mayo Clinic Criteria (11):
  - Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
  - Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture*.

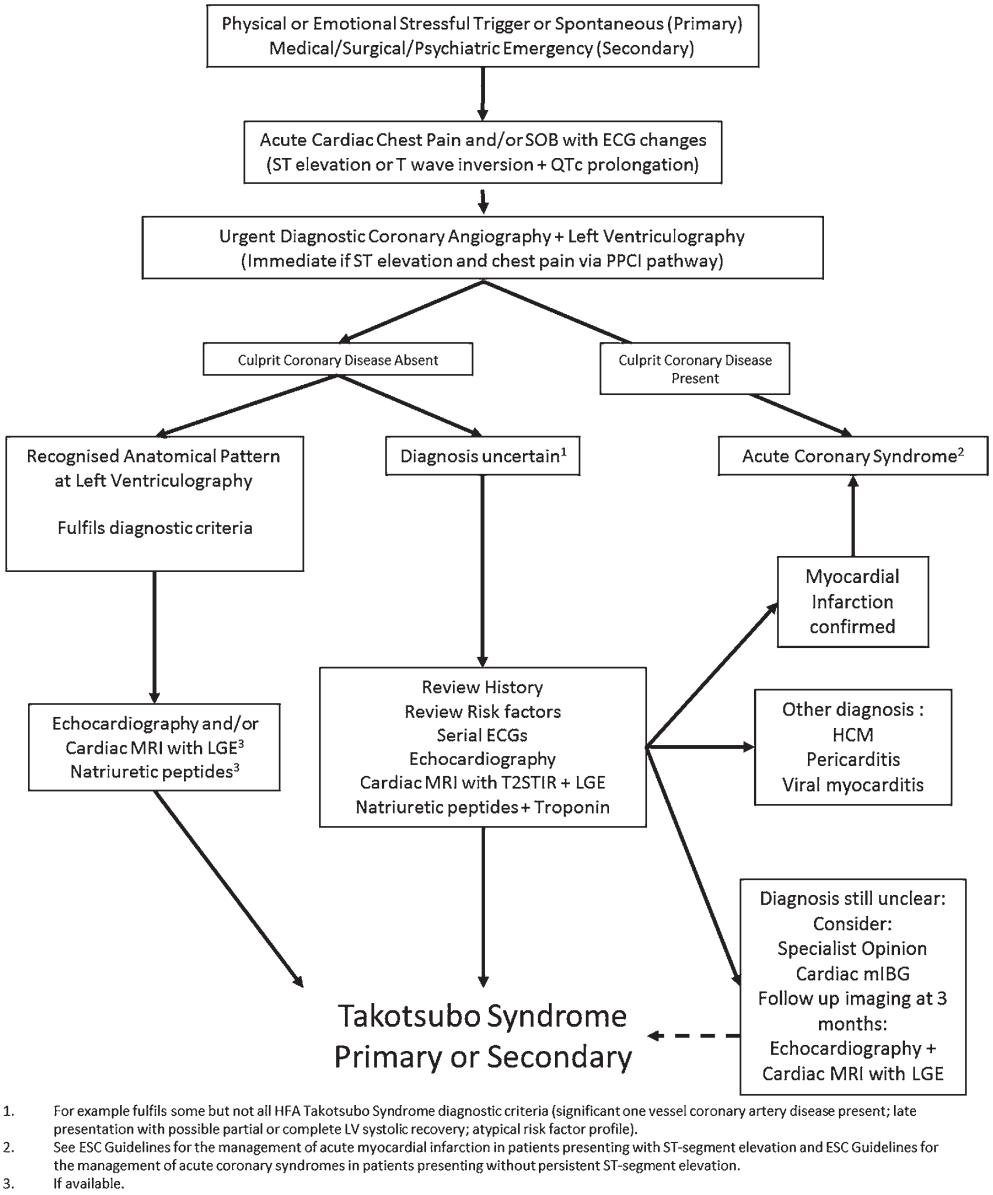
- New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
- Absence of pheochromocytoma and myocarditis.

* It is usual to find obstructive coronary disease, but the wall motion affection usually extends beyond a single coronary artery region, so it doesn't exclude the diagnosis.

- **Complementary tests**: there are a lot of complementary tests that can be practiced when TTS is suspected, but following Mayo Clinic Criteria, the most useful tests are:
  - EKG: the most frequent finding is changes in repolarization in precordial leads. In order of frequency we find ST elevation, T-wave invertion and QTc prolongation (4,12). The changes in ST segment usually are resolved in the first hours but changes in T-wave and QTc segment persist in subacute period (3).
  - Echocardiography: it shows the wall motion abnormalities, the dynamic obstruction of left ventricle outflow, mitral regurgitatation and intracavitary thrombus (4). The LVEF is reduced but the patients rarely present heart failure symptoms (5).
  - Coronary angiography and left ventriculography: it has to be done in every case to exclude coronary obstructive disease and the ventriculography can also show the wall motion abnormalities. We have to take into account that we are in front of elderly patients, so it is probable to find obstructive coronary disease, but we have to evaluate if it is enough to cause the degree of pattern of left ventricle dysfunction (5).
  - Cardiac magnetic resonance imaging (CMRI): it is used to value the cardiac perfusion and also gadolinium enhancement to exclude myocarditis. It should be considered in the first 7 days in all the patients with TTS (5).
  - Lab tests:
    - BNP: it is a biomarker that increase its levels in heart failure, and in TTS it is almost always elevated (2,5,12).

- Troponin I (Tn-I) and creatinine kinase muscle-brain (CK-MB): usually there is a moderate elevation of this necrosis biomarkers (>90% of the cases) but it is lesser than an ACS (2,4,5,12).
- Cathecolamines (epinephrine and norepinephrine (NE)): there is an increase in catecholamine serum level (4) that is two or three time higher than those patients with acute coronary syndrome at admission (2,5).

- Other:
  - CA-125: there is an article that suggest that CA-125 could be a prognosis factor. They found that higher levels of CA-125 are related to major adverse events (13).
  - Iodine – 123 – metaiodobenzylguanidine (^{123}I-MIBG): in the acute phase, there is reduced ^{123}I-MIBG in the myocardium affected part that reflect the sympathetic neural activity disturbance (5,12).
  - PET: it is used to value alterations of cardiac metabolism. It shows abnormal glucose metabolism (5).



1. For example fulfils some but not all HFA Takotsubo Syndrome diagnostic criteria (significant one vessel coronary artery disease present; late presentation with possible partial or complete LV systolic recovery; atypical risk factor profile).
2. See ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation and ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.
3. If available.

Figure 2. Diagnosis algorithm (5). LGE = late gadolinium enhancement; HCM = hypertrophic cardiomyopathy.

F. DIFFERENTIAL DIAGNOSIS

It is important to exclude some pathologies before the diagnosis of TTS. The main pathologies that can be confused with TTS are:

- **ACS**: the population who suffer from ACS are different than those who suffer from TTS, that are usually postmenopausal women as we have seen before, and its presentation can be the same. The most important difference is the finding of severe coronary obstruction with coronary angiography in ACS that can explain all

the symptoms. There are other differences in biomarkers, like CK-MB and Tn-I, that are higher in ACS and also in ECG findings (2).

- **Myocarditis**: we can differentiate TTS from myocarditis with CMRI because there is a delayed enhancement with gadolinium in myocarditis that will not be found in TTS (5).
- **Pheocromocytoma**: it releases catecholamines that can stimulate cardiac adrenoceptors and simulate a TTS. Clinically, the patients present hypertension, palpitations, diaphoresis and episodic headaches (2). Some authors suggest not to exclude pheocromocytoma to diagnose TTS and consider it as a possible comorbidity of this patients (14).

G. TREATMENT

There is a lack of evidence in treatment of TTS, but most of the hospitals use supportive care in the acute phase. Patients with TTS must be in an intensive care unit at least 24 hours, and most of them stay between 3 – 7 days in hospital. It has been used ß-blockers and angiotensin converter enzyme inhibitors (ACEI) that promote an early recovering of heart muscle once the patient is stabilized (15,16).

In case of cardiopulmonary failure it has been used extracorporeal membrane oxygenator or intra-aortic balloon pumping, but they are exceptional measures (17,18).

1.1.2 PROGNOSIS AND COMPLICATIONS

This syndrome has been always thought to be benign, but the last evidence show that its mortality rate is similar (19) or higher (20) to ACS, but the majority of the cases are due to non-cardiovascular causes (13,21). Timelines of cardiac motility alterations recovery vary depending on the severity, but the mean is 12 weeks. The ECG changes and BNP levels persist altered 6 – 12 months and in some cases can remain permanently abnormal (5). It is not unusual the recurrence of TTS in the first 3 months – 1 year and it can affect the same wall part or a different part.

Some studies have concluded some factors of worse prognosis (7):

- Physic stress trigger (22,23): it has higher mortality rate and the authors suggest that could be because of the magnitude and duration of adrenergic exposure and the contribution of systemic inflammation (7).
- Men (21).
- ≥75 years old (21).
- LVFE ≤35%: in general there are more complications and mortality (see Table 4) (21,24).

Table 3. Differences between patients with LVEF ≤ or > 35% (24)

	LVEF ≤35%	**LVEF >35%**
Arrhythmias	More risk	Less risk
Cardiogenic shock	More frequent	Less frequent
Respiratory support	More frequent	Less frequent
Mortality	Higher	Lower
Clinic presentation	More chest pain	

- Killip III - IV at admission (20).
- Diabetes mellitus (20).
- Glomerular filtration rate <60 mL/min (24).
- High troponin levels (23).

– Acute neurological or psychiatric disease (23).

Other articles suggest to classify the patients between high or low risk and follow a different algorithm (3,5). They consider higher risk patients those with at least 1 major or 2 minor risk factors (5).

Table 4. Heart Failure Association risk stratification in Takotsubo syndrome (5)			
Risk Factor		**Higher risk**	**Lower risk**
MAJOR RISK FACTORS			
Age		≥75 years	See minor risk factors[a]
Systolic blood pressure		<110 mmHg	≥110 mmHg
Clinical pulmonary oedema[b]		Present	Absent
Unexplained syncope, ventricular tachycardia or ventricular fibrillation		Present	Absent
LVEF		<35%	See minor risk factors[a]
Left ventricular outflow tract obstruction		≥40 mmHg	Absent o <40 mmHg
Mitral regurgitation[c]		Present	Absent
Apical thrombus		Present	Absent
New ventricular septal defect or contained left ventricle (LV) wall rupture		Present	Absent
MINOR RISK FACTORS			
Age		70 – 75 years	<70 years
ECG	**QTc**	≥500 ms	<500 ms
	Pathological Q waves	Present	Absent

	Persistent ST elevation[d]	Present	Absent
LVEF		35 – 45%	≥45%
Physical stressor		Present	Absent
Natriuretic peptides	**BNP**	≥600 pg/mL	<600 pg/mL
	NT-proBNP	≥2000 pg/mL	<2000 pg/mL
Bystander obstructive coronary artery disease		Present	Absent
Biventricular involvement		Present	Absent

[a]See minor criteria regarding LVEF in the absence of major criteria. [b]Lower zone (basal) pulmonary rales on clinical examination or evidence on chest X-ray. [c]Moderate or severe mitral regurgitation. [d]≥3 years. BNP = brain natriuretic peptide, LVEF = left ventricle ejection fraction, NT-proBNP = N-terminal pro-brain natriuretic peptide.

In 52% of patients there are complications (acute phase and 5 years follow-up) (5). The most common complication is heart failure (30%). Other complications are: thrombus in left ventricle, obstruction of left ventricle outflow, mitral regurgitation, ventricular arrhythmias (due to QTc prolongation), cardiogenic shock, left ventricle wall rupture and death (3,23).

Nuñez Gil et al evaluated complications of TTS in Spanish population and they used major adverse cardiac events (MACE), that includes re-admission, new symptoms and dead. They saw an incidence of 6,5% of MACE in 1 year of follow-up (6). In another article, that took into account recurrence of Takotsubo, acute myocardial infarction (AMI), stroke or transient ischemic attack and death of any cause found an incidence of 9,9% in 1 year of follow-up (25).

1.1.3 SPECT AND ^{123}I-MIBG

Nuclear medicine is a medic speciality that uses radioactive isotopes non-encapsulated to diagnose, treat or investigate. The image diagnose in nuclear medicine is based in the morphologic and functional analysis of the organ studied due to the detection of γ radiation emitted by a radiopharmaceutical administered previously to the patient (26).

Simple photon emission computed tomography (SPECT) is a type of nuclear medicine imaging test that provide 3D images of the distribution of radioactive tracer molecules that emit gamma rays. The gamma rays are detected by gammacameras that rotate around the patient's body to record images in different angles and generate the 3D images (27).

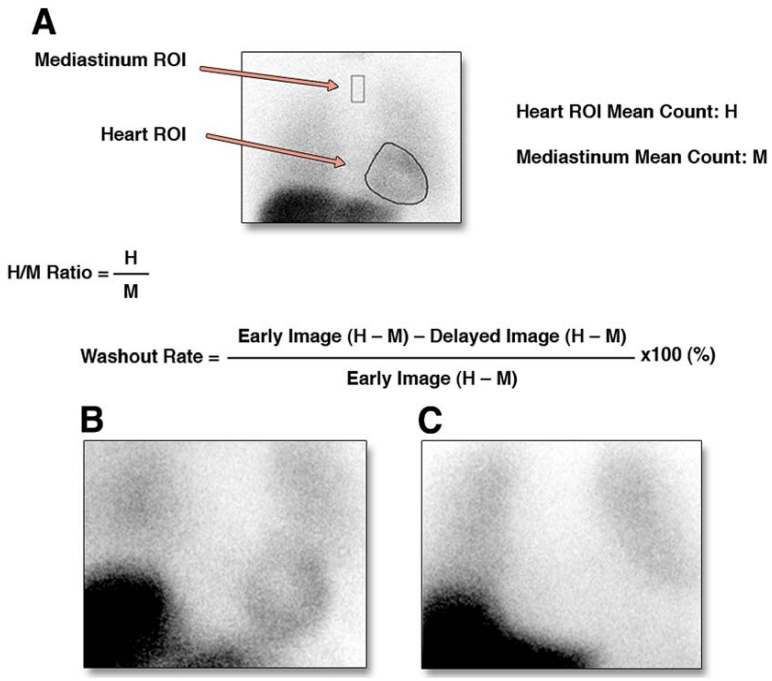
There is a type of SPECT that uses ^{123}I-MIBG and it was developed to study patients with heart failure (HF). To understand how ^{123}I-MIBG works, we need to know that it is related with NE and in TTS there is an increase of NE in the synaptic cleft. NE is re-uptaked mainly by transporter 1 (uptake 1) (there is an uptake 2 transporter but it has low activity in humans). In patients with HF uptake 1 transporter is downregulated and consequently there is more NE in synaptic cleft and less NE in pre-synaptic nerve ending. This hyperadrenergic state produces a downregulation of ß-adrenergic receptors that are present in the myocardium (which reduces cardiac contractility) (28–30).

^{123}I-MIBG has a similar molecular structure to NE and it acts selectively on sympathetic nerves ending with the same uptake, storage and release process as NE except that it is not metabolised by monoamine oxidase and it does not have effect in post-synaptic receptors. Thus, it will reflect the status of catecholamine storage in pre-synaptic fibres (29,30).

A complete standard protocol consists in acquisition of early and late planar images, 15 minutes and 4 hours after intravenous injection of ^{123}I-MIBG respectively. There are two main measures used to evaluate neuronal activity:

- Heart-to-mediastinum ratio (H/M) that is calculated after drawing regions of interest over the heart and the mediastinum (see Figure 3). It reflects cardiac sympathetic activity.

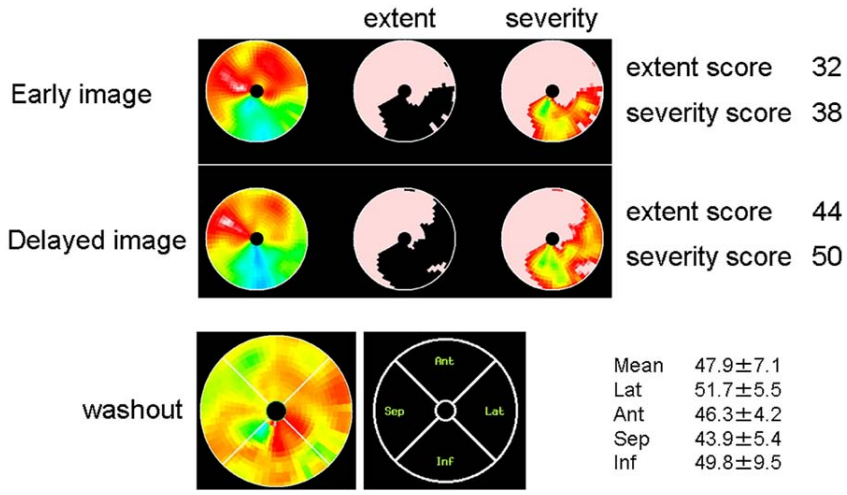
– Wash-out rate (WR) that is calculated comparing early and delayed activities (see Figure 3). It reflects NE retention by sympathetic neurons.



(A) Calculation of *meta*-iodobenzylguanidine (*m*IBG) heart-to-mediastinum ratio (HMR) and wash-out rate on an anterior view of the thorax. Regions of interest (ROI) are drawn overt the heart and mediastinum. (B) Normal cardiac *m*IBG activity in a patient with HMR: 1,80. (C) Severely decreased cardiac *m*IBG activity in a patient with HMR: 1,10.

Figure 3. Quantification of cardiac ^{123}I-MIBG activity (30)

We can also evaluate the extent and severity of the affection with a polar map of the myocardium where the apex is represented in the centre and the base in the periphery (see Figure 4). This polar map is usually divided in 17 segments (see Figure 5) (31).



The extent map displays in black the pixels with counts -2 standard deviations or less compared with the normal file. The severity map displays the defect severity, after dividing the total count difference between the black pixels and the normal region by the total number of pixels. The wash-out rate can be estimated for each segment as well as for the whole ventricle. Ant = anterior; Inf = inferior; Lat = lateral; *m*IBG = *meta*-iodobenzylguanidine; Sep = septal; SPECT = single-photon emission computed tomography.

Figure 4. Polar map display of the regional ^{123}I-MIBG distribution from a SPECT study (30)

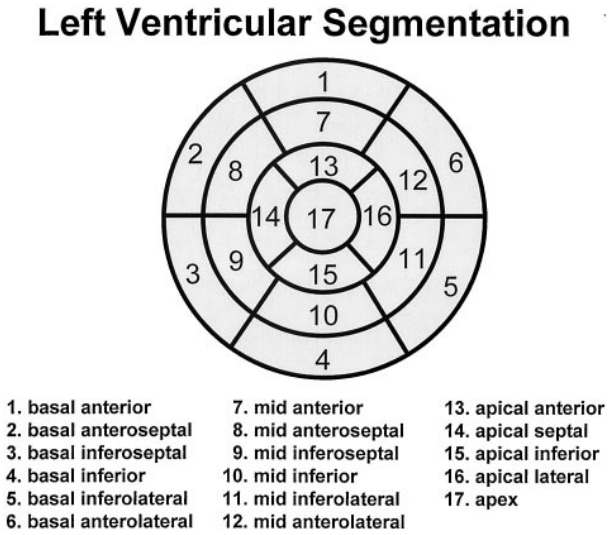


Figure 5. Segments of the LV in a polar map (31)

The H/M (mainly delayed images) is an independent prognosis factor for patients with heart failure, with a cut-off value of 1,80 (lower levels has worse prognosis) (30,32). One study found that patients with a WR ≥27% has also worse prognosis.

There are some pathologies that can interfere with the SPECT results:

- Diabetes mellitus, arrhythmias and dilated cardiomyopathy can have basal innervation impairment.
- AMI can reduce perfusion and consequently there will arrive less tracer to the myocardium.

The presence of any of these diseases prevents conclusive results of ^{123}I-MIBG SPECT, so it is useful to do a gated – SPECT (G-SPECT) with ^{99m}Tecnecium-sestamibi (^{99m}Tc-sestamibi) to evaluate cardiac perfusion.

Sestini et al performed SPECT with ^{123}I-MIBG in patients with TTS and followed them for 2 years. They found some differences in patients that were recovered and those that were not recovered in ^{123}I-MIBG perfusion (Table 6).

- In the acute phase, they found that patients that were not recovered after 1-2 years had greater impairment of cardiac perfusion, wall motion, sympathetic nerve impairment (see Figure 5) and WR. They also saw that these patients had lower LVEF.
- Not recovering patients were older, had a higher peak of Tn-I and present ST elevation in the EKG.
- After 1 month and 1-2 years not recovering patients continued having more affection of sympathetic nerve activity compared with recovering patients, which had normal ^{123}I-MIBG uptake after 1-2 years.

So, they conclude that adrenergic dysfunction is related with the initial impairment level and age at onset.

Table 5. Differences between recovered and not recovered patients (33)		
	Not recovering patients	**Recovering patients**
Cardiac perfusion, wall motion, sympathetic nervous system (SNS) functionality and WR	Lower	Higher
LVEF by SPECT	Lower	Higher
Clinic characteristics	Older, higher pick of Tn-I and more prevalence of ST elevation	
Topographic distribution of myocardial perfusion	More segments affected and all patients had apex affected	Less segments affected and only 54,5% of the patents had the apex affected
LV functionality	More segments affected	Less segments affected
SNS alterations (T0)	↓^{123}I-MIBG uptake in all patients in early and late images and more segments affected	↓^{123}I-MIBG uptake in all of them in late images but only 10/11 in early images. Less segments affected
SNS alterations (T1)	↓^{123}I-MIBG uptake in all patients in early and late images and more segments affected	↓^{123}I-MIBG in 7/11 patients in early images and 9/11 patients in late images. Less segments affected
SNS alterations (T2 and T3)	- T2: mild/moderate affection of apex. - T3: mild affection of apex.	Normal in all patients

*T0 = acute phase, T1 = 1 month, T2 = 1 year, T3 = 2 years.

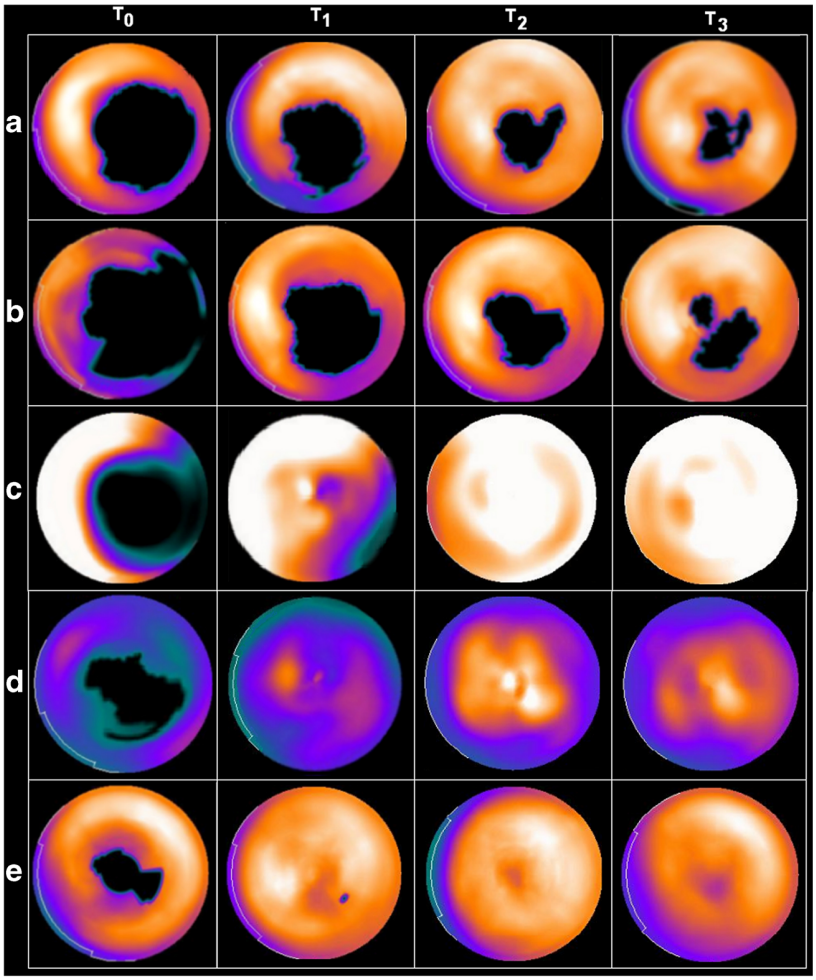


Figure 6. Polar map of not recovering patients (33)

1.2 JUSTIFICATION

TTS have always been thought to be a benign disease, but recent studies have shown that its complications are similar to patients who suffer ACS.

We have seen in the most recent literature that there is a relationship between catecholamine, TTS and impairment of the sympathetic nervous system. It is therefore useful to perform a SPECT with ^{123}I-MIBG to assess the degree and distribution of the impairment of sympathetic nervous system in the acute phase of TTS.

In a recent study done with SPECT and ^{123}I-MIBG, there were differences in the degree of the impairment between patients who normalized their ^{123}I-MIBG uptake and those who did not. But there is a lack of evidence if this innervation alteration related with recovery has consequences in clinic prognosis.

The aim of this study is to perform a SPECT with ^{123}I-MIBG in all the patients with TTS in the acute phase and do a prospectively record of all complications to conclude if there's a relationship between the initial distribution of ^{123}I-MIBG and prognosis.

The importance of doing this study is to find a high-risk pattern in patients that are more likely to have complications. This will allow us to recommend a different follow-up in high-risk patients as compared with those with a low-risk pattern.

2. HYPOTHESES

2.1 MAIN HYPOTHESIS

Patients with Takotsubo syndrome who have Total Defect Score >8 in the ^{123}I-MIBG SPECT have a higher risk of worse evolution in 3 years (more major adverse cardiac events) in comparison with the patients who have Total Defect Score ≤8.

2.2 SECONDARY HYPOTHESIS

- The incidence of each complication included in major adverse cardiac events is different between groups: Total Defect Score (TDS) >8 or ≤8.
- The incidence of MACE is higher in patients with more severe impairment.

3. OBJECTIVES

3.1 MAIN OBJECTIVES

The main objective is to find the relationship between the ^{123}I-MIBG pattern in the acute phase with prognosis (MACE), that include mortality of any cause, mortality of cardiovascular cause, acute myocardial infarction, new Takotsubo (recurrence) and re-admission.

- We will evaluate MACE at 30 days, 1 year and 3 years after the acute phase.
- One group will be patients with TDS >8 in the SPECT with ^{123}I-MIBG, that includes those patients with moderate and severe affection, and the other group patients with TDS ≤8, that includes patients with normal or mild affection.

3.2 SECONDARY OBJECTIVES

We are going to study two secondary objectives that will be:

- To analyse if there are differences of each of the complications included in MACE between groups defined by TDS: TDS >8 or ≤8.
- To analyse the severity of sympathetic cardiac nervous system impairment associated to MACE.

4. METHODS

4.1 STUDY DESIGN

This study is a prospective cohort, multi-centric study, with a consecutive method of sampling of patients attending the Coronary Unit with Takotsubo syndrome that meet inclusion criteria, with the purpose of comparing the prognosis between patients who have TDS >8 in the ^{123}I-MIBG SPECT and patients with TDS ≤8.

Data will be collected in the Cardiology Department of different hospitals from Catalonia.

4.2 STUDY POPULATION

The study population will include patients with TTS from Catalonia. All patients in this study will be newly-diagnosed for TTS.

- **Inclusion criteria**
  - Patients with Takotsubo syndrome diagnosed by Mayo Clinic criteria (11) **(see Annex 1)** in the Coronary Unit.
- **Exclusion criteria**
  - Pregnant woman.
  - Background of AMI, dilated cardiomyopathy, arrhythmias, diabetes mellitus or severe heart failure because they interfere in ^{123}I-MIBG SPECT results .
  - Refuse of informed consent.
  - Patients with terminal disease or another disease that could interfere in prognosis of patients with heart disease.
  - Patients that live in places with difficulties for follow-up.

4.3 SAMPLE

4.3.1 SAMPLING METHOD

A non-probabilistic consecutive sampling method will be performed for 2 years and 6 months.

The patients will be recruited at the Coronary Unit of Cardiology Department of 11 hospitals. Patients will be informed about the study after the acute treatment. The information document **(see Annex 2)** and the informed consent **(see Annex 3)** of the study will be given to all participants. They will only be included in the study if they sign and agree with the conditions of the research.

4.3.2 SAMPLE SIZE

Templin et al, found an incidence of MACE at 1 year of follow-up of 9,9% and they took into account recurrence of TTS, AMI, stroke or transient ischemic attack and death of any cause. We are not going to register cerebrovascular accidents but we will register re-admissions, so we have estimated the same percentage of complications in our population (25). We are going to follow-up our patients for 3 years, so our total percentage of complications will be 29,7%. We consider a significant difference between groups a reduction of 30% of complications in Group 2 (TDS $\leq$8) compared to Group 1 (TDS >8).

To calculate the needed sample, we used free online software called GRANMO ®.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 391 subjects are necessary in first group and 391 in the second to find as statistically significant a proportion difference of MACE, expected to be of 0.297 in patients with moderate and severe affection of SPECT pattern and 0.208 in patients with normal or mild affection of SPECT pattern. A drop-out rate of 5% has been estimated. The ARCSINUS approximation has been used. So, the total number of participants needed for the study is 782.

As there is no evidence about the incidence of MACE in each group and it is an approximation, we will review after 6 months of sample recruitment if it differs from our estimations and we will modify our sample size. We also have to take into account

that maybe not all the patients will accept participating in our study, in case it happens we will increase the time of subjects' recruitment.

We know that in Catalonia there is an incidence of 16.707 ACS/year and knowing that TTS is approximately 2% of all ACS we estimate an incidence of 334 TTS/year. Eleven hospitals with coronary unit from Catalonia will participate in our study: Hospital Arnau i Vilanova, Lleida; Hospital Verge de la Cinta, Tarragona; Hospital Universitari Doctor Josep Trueta, Girona; Hospital Germans Tries i Pujol, Badalona; Hospital del Mar, Barcelona; Hospital de la Santa Creu i Sant Pau, Barcelona; Hospitall Vall d'Hebron, Barcelona; Hospital clínic, Barcelona; Hospital de Sant Joan Despí Moisès Broggi, Barcelona; Hospital de Manresa, Manresa; Hospital Universitari General de Catalunya, Barcelona.

We will need 2 years and 4 months to complete the inclusion of our sample of subjects, but we have planned to do it for 2 years and 6 months taking into account that not everyone will be enrolled in the study.

4.4 MEASUREMENTS: VARIABLES

4.4.1 MAIN VARIABLES

- **Independent variable**: ^{123}I-MIBG pattern at diagnosis.

  We will have 2 groups of patients depending on the TDS score: GROUP 1 patients with TDS >8 (moderate or severe) and GROUP 2 patients with TDS ≤8 (normal or mild) (*see 4.5.1*).

- **Dependent variable**: MACE.

  Our dependent variable is the prognosis at 30 days, 1 year and 3 years after the diagnosis. We will define MACE as the occurrence of any of the following during the patients' follow-up: any death, death from cardiovascular cause, AMI, recurrence (new Takotsubo) and re-admission. Thus, this will be a combined variable. We will also analyse separately each of the complications between the two groups in order to see the differences between them.

  The follow-up data will be obtained from the hospitals, once patients have signed the informed consent of the study. In the informed consent, there is an explanation of the confidentiality and anonymity of patient information. Patients will get an appointment to be re-assessed after 30 days and an echocardiography will be performed and our clinical features (MACE) will be evaluated. Another appointment will be made after 1 year to perform a new CRMI, an echocardiography and register all incident complications. After 3 years an echocardiography will be performed and all incident complications will be registred.

4.4.2 SECONDARY VARIABLES

- **Confounding variables**: there are other variables that could affect our dependent and independent variables, but they are not the object of our study. As these variables could act as confounders we will have to control them in order to increase the internal and external validity of our study. This confounding effect of these variables can be minimized later with a multivariate analysis.
  - Age: years.
  - Sex: Male or Female.

- LVEF: we will consider preserved >52%, moderate 35 – 52% and severe <35%. Severe decrease in the ejection fraction on admission is related with worse prognosis.
- Physical trigger: endocrine diseases, haematology diseases, sepsis (*see Table 1*).
- Neurological or psychiatric disease.
- High troponin levels: it is defined as >2SD based on local references values.
- High levels of N-terminal pro-brain natriuretic peptide(NT-proBNP): it is defined as >2SD based on local references values.
- Increased risk for cardiovascular disease: we will define it using the online calculator REGICOR, that defines high risk when it is 10 – 14.9% at 10 years (34). It takes into account tobacco, diabetes mellitus, cholesterol, blood pressure, age and sex.

– **Others**:

- Mortality from cardiovascular cause: defined as all deaths produced by AMI, sudden death or cardiac failure.
- Mortality from any cause.
- AMI: defined as compatible clinical + ECG changes + elevation of biomarkers of myocardial necrosis (creatinine kinase (CK) and Tn).
- New Takotsubo (recurrence)**.**
- Re- admission.
- Severity of sympathetic cardiac nervous system impairment: we will use a 5-point system to evaluate the severity of the affection and we will calculate the percentage of segments in each category:
  - 0 = normal.
  - 1 = mildly reduced ^{123}I-MIBG uptake.
  - 2 = moderately reduced ^{123}I-MIBG uptake.
  - 3 = severely reduced ^{123}I-MIBG uptake.
  - 4 = absence of ^{123}I-MIBG uptake.

4.5 DATA COLLECTION

4.5.1 FIRST EVALUATION

For the diagnosis of TTS, we will use Mayo Clinic criteria **(see Annex 1)**.

We will perform an echocardiography in the acute phase to assess the wall motion abnormalities and LVEF (calculated by Simpson's method), a coronary catheterization and ventriculography, a 12-derivations EKG, blood analysis (haemogram, cholesterol, HbA1c, CK, CK-MB, Tn-I, NT-proBNP) and a CMRI with gadolinium (cine sequences, short time inversion recovery sequences, first step perfusion and delayed enhancement) **(see Annex 5)**.

Before performing the SPECT with ^{123}I-MIBG, we will carry out a G-SPECT with ^{99m}Tc-sestamibi to evaluate cardiac perfusion. It has to be done 1 or 2 days before the SPECT with ^{123}I-MIBG. We will also ask the patients about medication to see if they take any of the drugs that can interfere in ^{123}I-MIBG SPECT results and stop them 48 hours before doing it (35) **(see Annex 10)**.

We will perform the SPECT with ^{123}I-MIBG after the patient has signed the informed consent **(see Annex 4)** within the first 3 days. Those hospitals that do not have SPECT will refer their patients to the nearest hospital with SPECT.

As Sestini et al did in their study, we will give 130 mg of potassium iodine 1h before tracer injection to block thyroid iodine uptake. Then 200 MBq of ^{123}I-MIBG will be injected intravenously, and planar anteroposterior images and SPECT tomographic acquisition of the chest will be obtained 15 (early) and 220 (late) min after tracer injection. Images will be interpreted by one experienced observer in each centre.

We will quantify ^{123}I-MIBG uptake using the early and late H/M and we will consider it to be normal when it is $>2.02 \pm 0.2$ and 2.10 ± 0.24, respectively. We will also quantify WR and we will consider it to be normal when it is <10%.

We will present SPECT images in a polar map with 17 segments and we will calculate ^{123}I-MIBG uptake defects as a percentage of the whole ventricle.

After that, each segment will be scored with a 5-point system (0= normal; 1= mildly reduced; 2= moderately reduced; 3= severely reduced; 4= absence of uptake).

We will calculate the TDS for each patient which reflects the number of segments affected:

- TDS <4 → normal.
- TDS 4 – 8 → mildly abnormal.
- TDS 9 – 13 → moderately abnormal.
- TDS >13 → severely abnormal.

We will establish two groups: *Group 1*, that includes the patients with a TDS >8 and *Group 2*, that includes the patients with TDS ≤8. TDS will be calculated for late images.

We will also calculate the severity of the impairment of sympathetic activity calculating the percentage of segments present in each category of the 5-point system. For further clarification **see Annex 11**.

Once the patient is stabilized, we will perform an exhaustive interview and physical examination. We will ask about the trigger, to find out if there was an emotional trigger or a physical trigger. We will also ask about cardiovascular risk factors to estimate the risk using the REGICOR calculator: tobacco, diabetes mellitus, hypercholesterolemia and blood pressure.

Before leaving the hospital, we will program a first appointment 30 days later.

4.5.2 TREATMENT

We will treat all the patients in the acute phase following current Clinical Practice Guidelines. When they are stabilized we will give them 100 mg/day of acetylsalicylic acid and ACEI provided that they are well tolerated.

4.5.3 FOLLOW-UP

We will evaluate MACE at 30 days, 1 year and 3 years in order to study if there are differences in the outcomes between the different ^{123}I-MIBG patterns assessed in the acute phase.

After 30 days of the event we will perform an echocardiography to evaluate LVEF and wall motion abnormalities and we will register MACE **(see Annex 6)**.

After 1 year of the event, we will perform the common follow-up of a patient with TTS with a CRMI and an echocardiography and we will register again MACE **(see Annex 7)**.

After 3 years, we will perform an echocardiography and the register of MACE for the last time **(see Annex 8)**.

4.6 STATISTICAL ANALYSES

The data will be analysed using IBM SPSS ® for Windows ®. P value will be considered statistically significant when <0,05.

4.6.1 UNIVARIATE ANALYSIS

The main variables of our study are both qualitative and categorical. Regarding secondary variables, some are qualitative and other quantitative.

- For qualitative categorical variables, results will be expressed as percentages and proportions.
- For quantitative variables, we will describe them as mean ± standard deviation (those with normal distribution) and with median and interquartile range (25-75) (those without normal distribution).

4.6.2 BIVARIATE ANALYSIS

Percentages for categorical variables will be shown in a contingency table and chi square test (x^2) will be used to compare prognosis of patients after 3 years in both group, the group with moderate and severe impairment in the SPECT and the group with normal or mild impairment in the SPECT in the acute phase. It will be also calculated at 30 days and 1 year, but we will not have conclusive results because sample size has not been calculated for the incidence of complications at that moment.

For the secondary objectives, we will also use contingency table and chi square test (x^2) as all the variables are qualitative variables.

The relative risk will be estimated for both groups defined by TDS: TDS >8 and TDS ≤8.

To analyse the patients' characteristics of the two groups (quantitative covariates), t-student test (normal distribution) or Mann-Whitney (without normal distribution) will be used. To compare variables with ≥3 categories, ANOVA (normal distribution) or Kruskal-Wallis test (without normal distribution) will be performed to test differences.

4.6.3 MULTIVARIATE ANALYSIS

A COX model will be used to analyse the association between the exposure variable and the outcome variable. These variables are patients undergoing TTS with sympathetic activity impairment in the SPECT with ^{123}I-MIBG performed in the acute phase and incidence of MACE at 3 years after the acute phase. The logistic model analysis will be adjusted for statistically significant covariates in order to adjust for potential confounding variables.

5. WORK PLAN AND CRONOGRAM

The research team will include different specialists, who have long experience, not only in the research, but also in the use and interpretation of the diagnostic techniques that will be used in our study. There will be specialists from the Cardiology Unit, Radiology Unit and Nuclear Medicine Unit from every hospital. A statistician and a data manager will be hired for statistical analysis and data collection, respectively. The whole project will last for 6 years and 9 months.

5.1 TASK 1: PROTOCOL DEVELOPMENT (4 MONTHS)

The protocol of the study will be completed with the collaboration of all the research team. Before carrying it out, approval by the ethical committee (CEIC) will be needed.

5.2 TASK 2: INITIAL COORDINATION (1 MONTH)

We will meet with all the participants of the study. In that meeting we will define the role of each participant and create a chronogram to clarify the different phases of the study.

We will program new meetings during the study to evaluate if there are problems and make modifications if they are needed. All the team will be in contact via e-mail in case there is a need to solve unexpected problems.

During the first meeting, we will also have two informative courses to standardize the measures, one for nuclear medicine specialists and another for echocardiographists.

5.3 TASK 3: DATA COLLECTION (5 YEARS AND 6 MONTHS)

- **Recruitment of subjects**: it will last for 2 years and 6 months and it will consist in recruitment of patients meeting the inclusion criteria. Once the patient is stabilized, the information sheet and information consent will be facilitated to the patients.
- **Data collection**: it will last for 3 years. The cardiologist of each centre will be the responsible for data collection. Every 6 months, we will assess with repeated measurements that all operators are taking the same measurements, and if there

are differences we will standardize them again. We will also have one person who will be responsible in every centre for every technique and who will revise the data. We will contract a data manager that will revise if the data collection is done correctly and that everything is properly annotated.

5.4 TASK 4: DATA ANALYSIS AND FINAL REPORT (4 MONTHS)

Once the data collection is finished according to our sampling, the whole data will be organized in the database by the data manager. Also, the necessary univariate, bivariate and multivariate analyses will be performed by the statistician in this period.

A final meeting will be done with all the research team to discuss the results. The final report will be prepared by the main research team once the data have been analysed.

5.5 TASK 5: PUBLICATION AND DISSEMINATION OF RESULTS (6 MONTHS)

This will be done by the research team once the data has been analysed and concluded. The final article will be published in a medical journal in order to properly disseminate the results of the study.

TASKS	2018		2019				2020	2021			2022	2023	2024			2025			PERSONNEL
	11	12	1	2	3	4 to 12		1 to 10	11	12			1 to 10	11	12	1	2	3 to 8	
TASK 1: PROTOCOL DEVELOPMENT																			
1. Literature review																			All research team
2. Protocol elaboration																			Main researchers
TASK 2: INITIAL COORDINATION																			
3. First meeting																			All research team
4. Course to standarize measurements																			Clinical researchers
TASK 3: DATA COLLECTION																			
5. Subjects recruitment																			Clinical researchers
6. Data collection																			
TASK 4: DATA ANALYSIS AND FINAL ELABORATION																			
7. Enter data in a database.																			Data manager
8. Evaluation of correct data collection																			
9. Data entry in SPSS statistics																			Statistical consulting
10. Statistical analysis																			
11. Analysis of the results and discussion																			All research team
12. Conclusion																			
13. Final report elaboration																			Main researchers
TASK 5: PUBLICATION AND DISSEMINATION OF RESULTS																			
14. Publication in medical journals																			Main researchers

6. ETHICAL CONSIDERATIONS

This research protocol will be presented to the Clinical Research Ethical Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of every hospital that participate in the study. They will assess if the study fulfils the required criteria of being approved. Moreover, the recommendations given by the committee will be taken into account to carry out the study.

The project will be carried out according the ethical principles established by World Medical Association in the *Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects* (last actualization October 2013). Furthermore, we will take into consideration the Spanish Organic Law *14/2007, de Investigación Biomédica*, which regulates biomedical investigation involving human beings in Spain.

It will be compulsory to have the Management Department's approval from all the hospitals participating in the study.

Every patient will be properly informed and they will receive the information sheet about the study **(see Annex 2)**. Then, they will sign voluntarily the informed consent **(see Annex 3)**. Participants have the right to withdraw the consent without having a negative effect on the relationship with their assigned doctor or treatment received. The principle of autonomy will be respected in all the process.

According to "*Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal*", personal and clinical information of participants will be kept confidential at all times and only be used for the purpose of the research. Moreover, all data will be analysed anonymously. Participants will have to sign voluntarily the informed consent before being included in the study after receiving appropriate information about procedures, according to "*Ley 41/2002 Básica reguladora de la autonomia del paciente y de derechos y obligaciones en material de información y documentación clínica*".

All the investigators will have to declare no conflict of interest.

7. STUDY LIMITATIONS

There are some potential limitations that should be considered before starting our study in order to limit them:

- As we use a consecutive sampling method, we could have a selection bias that we will try to avoid using inclusion and exclusion criteria. Only the patients who fulfils the inclusion criteria and do not meet any of the exclusion criteria will be invited to participate in the study.
- TTS is a disease with low incidence. To achieve conclusive results, we have designed a multicentre study.
- We can have an information bias due to possible loss of participants during the follow-up as we have a long period of follow-up. We will solve this possible bias with follow-up calls via telephone for all patients who do not attend to the medical appointments.
- We have taken into account all the possible confounders known after an exhaustive bibliography research. Nevertheless, there may be other confounding variables not recorded that can be the objective of further studies.
- We realise that the best study design should be a case-control study because TTS is a low incidence disease with low incident complications, but this design will not allow us to see how complications develop over time.

8. BUDGET

8.1 PERSONNEL

Most of the activities in the study (bibliography research, protocol redaction, data collection and publication) will be done by the research team, so it will not generate an extra-cost.

We will need a qualified statistician in order to analyse all the data during data analysis period.

We will hire a data manager, due to the fact that we will carry out a multicentre study and a constant revision of the information is needed. We estimate 20 hours/week of work coordination.

8.2 MATERIAL AND SERVICES

All the tests that will be performed for the diagnose of TTS are included in the normal hospital practice so it will not generate an additional cost.

We should include in our budget the SPECT with ^{123}I-MIBG that will be performed in the acute phase. It costs 350€ per patient.

We should also include the G-SPECT with ^{99m}Tc-sestamibi that will be performed and it costs 135€.

The echocardiographies and the second CMRI that will be performed after 1 year of follow-up are not included in the budget because it is part of the usual follow-up in a patient with TTS.

The budget does not include material office supplies and software (SPSS® or Microsoft Windows®) because all the centres have the correspondent license.

8.3 MEETINGS

Before starting data collection, we will do one meeting to standardize the measures between all the centres.

We will do periodic meetings with all the hospitals and in order to reduce the cost, this will be done by videoconference (there will be a room with electronic devices). In every meeting, one cardiologist of each centre will be representing the whole unit.

There will be a last meeting that will be done in Hospital Universitari Josep Trueta to discuss the findings where one cardiologist of every unit will be present.

8.4 PUBLICATION AND DISSEMINATION RESULTS

We will try to publish our study in *Journal of the American Collegue of Cardiology (JACC)*.

This project will be presented at the "*Sociedad Española de Cardiología"* and "*European Society of Cardiology"* congresses.

	Price per unit	Amount	Total
PERSONNEL			
Statistician	25 €	100	2.500 €
Data manager	20.000€/year	3 years	46.800 €
MATERIALS AND SERVICES			
SPECT with 123I-MIBG	350 €	782	273.700 €
G-SPECT with 99mTc-sestamibi	135 €	782	105.570 €
MEETINGS			
First meeting	1.500 €	1	1.500 €
Standardization course	3.000 €	2	6.000 €
Final conclusion meeting	1.500 €	1	1.500 €
PUBLICATIONS AND DISSEMINATION			
Publication cost	700 €	1	700 €
"Sociedad Española de Cardoiologia" congress	800 €	2	1.600 €
"European Society of Cardiology" congress	1.000 €	2	2.000 €
		TOTAL	442.000 €

9. FEASIBILITY

This study will be done in 11 centres from Catalonia, that have the necessary equipment to do the project. We need to take into account that due to the low incidence of TTS, it will take more than ten years to collect all the needed sample to have conclusive results if it is only done in Girona. On the other hand, there is a risk to obtain not statistically significant results.

We realise that is difficult to get 782 patients with TTS for our study, but as there is no evidence about prognosis in this disease and it is worth to have this information to do a different follow-up in patients with higher risk of worse prognosis to avoid complications. So, it justifies the effort that we will have to do.

10. BIBLIOGRAPHY

1. RETAKO [Internet]. Cardiopatia de estrés o síndrome de Tako-Tsubo: conceptos actuales. Madrid: Sociedad Española de Cardiologia; 2013 [cited 2017 Nov 23]. p. 1–6. Available from: http://www.retako.com/about.html

2. Ono R, Falcão LM. Takotsubo cardiomyopathy systematic review: Pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy [Internet]. Vol. 209, International Journal of Cardiology. Elsevier; 2016 [cited 2017 Nov 23]. p. 196–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26896623

3. Morales-Hernández AE, Valencia-López R, Hernández-Salcedo DR, Domínguez-Estrada JM. Síndrome de Takotsubo. Med Interna Mex [Internet]. 2016;32(4):475–91. Available from: http://www.medigraphic.com/pdfs/medintmex/mim-2016/mim164m.pdf

4. Núñez-Gil IJ, Mejía-Rentería HD, Martínez-Losas P. Practical update of Takotsubo syndrome. Med Clínica (English Ed. 2016;146(5):212–7.

5. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: A Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Vol. 18, European Journal of Heart Failure. John Wiley & Sons, Ltd; 2016. p. 8–27.

6. Núñez Gil IJ, Andrés M, Almendro Delia M, Sionis A, Martín A, Bastante T, et al. Caracterización del síndrome de tako-tsubo en España: resultados del registro nacional RETAKO. Rev Española Cardiol [Internet]. 2015 [cited 2017 Nov 23];68(6):505–12. Available from: http://appswl.elsevier.es/watermark/ctl_servlet?_f=10&pident_articulo=90429500&pident_usuario=0&pcontactid=&pident_revista=25&ty=83&accion=L&origen=cardio&web=www.revespcardiol.org&lan=es&fichero=25v68n06a90429500pdf001.pdf&anuncioPdf=ERROR_publi_pdf

7. Yalta K, Yalta T. Physically triggered takotsubo cardiomyopathy has a worse prognosis: Potential roles of systemic inflammation and coronary slow flow phenomenon. Vol. 242, International Journal of Cardiology. 2017. p. 31–2.

8. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. Vol. 135, Circulation. American Heart Association, Inc.; 2017. p. 2426–41.

9. Ghadri JR, Cammann VL, Napp LC, Jurisic S, Diekmann J, Bataiosu DR, et al. Differences in the Clinical Profile and Outcomes of Typical and Atypical Takotsubo Syndrome. JAMA Cardiol [Internet]. 2016 Jun 1 [cited 2017 Nov 23];1(3):335. Available from: http://cardiology.jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2016.0225

10. Murugiah K, Wang Y, Desai NR, Spatz ES, Nuti S V, Dreyer RP, et al. Trends in Short- and Long-Term Outcomes for Takotsubo Cardiomyopathy Among Medicare Fee-for-Service Beneficiaries, 2007 to 2012. JACC Hear Fail [Internet]. 2016 [cited 2017 Nov 23];4(3):197–205. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5323042/pdf/nihms735961.pdf

11. Scantlebury DC, Prasad A. Diagnosis of Takotsubo Cardiomyopathy. Circ J [Internet]. 2014 [cited 2017 Dec 1];78(9):2129–39. Available from: https://www.jstage.jst.go.jp/article/circj/78/9/78_CJ-14-0859/_pdf

12. Gopalakrishnan P, Zaidi R, Sardar MR. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. World J Cardiol [Internet]. 2017 [cited 2017 Nov 23];9(9):723–30. Available from: http://www.wjgnet.com/1949-8462/full/v9/i9/723.htm

13. Santoro F, Ferraretti A, Musaico F, Di Martino L, Tarantino N, Ieva R, et al. Carbohydrate-antigen-125 levels predict hospital stay duration and adverse events at long-term follow-up in Takotsubo cardiomyopathy. Intern Emerg Med. 2016;11(5):687–94.

14. Santoro F, Ferraretti A, Tarantino N, Di Biase M, Brunetti ND. Pheochromocytoma: Still an exclusion criterion for Tako-tsubo cardiomyopathy diagnosis? Int J Cardiol. 2015 Dec 15;201:32.

15. Medscape [Internet]. Tomich EB. Takotsubo Cardiomyopathy Treatment & Management; 2017. New York: Medscape; 2018 [cited 2017 Nov 24]. p. 1–3. Available from: https://emedicine.medscape.com/article/1513631-treatment

16. Harvard Health Publishing [Internet]. Takotsubo cardiomyopathy (broken-heart syndrome) - Harvard Health; 2016. Boston: Harvard University; 2018 [cited 2017 Nov 24]. p. 1–4. Available from: https://www.health.harvard.edu/heart-health/takotsubo-cardiomyopathy-broken-heart-syndrome

17. El-Battrawy I, Lang S, Ansari U, Sattler K, Behnes M, Schramm K, et al. Incidence and Prognostic Relevance of Cardiopulmonary Failure in Takotsubo Cardiomyopathy. Sci Rep [Internet]. 2017 [cited 2017 Nov 23];7(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5676737/pdf/41598_2017_Article_15327.pdf

18. Nagata T, Mohri M. The Clinical Features and Outcomes of Patients with Takotsubo Syndrome: The Experience at an Emergency General Hospital. Intern Med [Internet]. 2017 [cited 2018 Jan 10];Epub ahead:1–5. Available from: https://www.jstage.jst.go.jp/article/internalmedicine/advpub/0/advpub_9249-17/_pdf/-char/en

19. Tornvall P, Collste O, Ehrenborg E, Järnbert-Petterson H. A Case-Control Study of Risk Markers and Mortality in Takotsubo Stress Cardiomyopathy. J Am Coll Cardiol [Internet]. 2016 [cited 2017 Nov 23];67(16):1931–6. Available from: http://www.sciencedirect.com/science/article/pii/S0735109716008238?via%3Dihub

20. Vriz O, Brosolo G, Martina S, Pertoldi F, Citro R, Mos L, et al. In-hospital and long-term mortality in Takotsubo cardiomyopathy: a community hospital experience. J Community Hosp Intern Med Perspect [Internet]. 2016 [cited 2017 Nov 23];6(3):31082. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4942542/pdf/JCHIMP-6-31082.pdf

21. Stiermaier T, Moeller C, Oehler K, Desch S, Graf T, Eitel C, et al. Long-term excess mortality in takotsubo cardiomyopathy: predictors, causes and clinical consequences. Eur J Heart Fail [Internet]. 2016 [cited 2017 Nov 23];18(6):650–6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/ejhf.494/full

22. Desai SK, Shinbane J, Das JR, Mirocha J, Dohad S. Takotsubo Cardiomyopathy: Clinical Characteristics and Outcomes. Rev Cardiovasc Med. 2015;16(4):244–52.

23. Kato K, Lyon AR, Ghadri J-R, Templin C. Takotsubo syndrome: aetiology, presentation and treatment. Heart. 2017 Sep 1;103(18):1461–9.

24. El-Battrawy I, Ansari U, Lang S, Behnes M, Schramm K, Fastner C, et al. Impact and management of left ventricular function on the prognosis of Takotsubo syndrome. Eur J Clin Invest. 2017 Jul;47(7):477–85.

25. C. Templin TFL et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med [Internet]. 2015 [cited 2017 Nov 28];10373(3):929–38. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1406761

26. Cabrero Fraile FJ. Fundamentos del diagnóstico por imagen en medicina nuclear. In: Cabrero Fraile FJ, editor. Imagen Radiológica: principios físicos e instrumentación. Barcelona: Elsevier; 2004. p. 232–75.

27. National Institute of Biomedical Imaging and Bioengineering [Internet]. Nucelar Medicine; 2016. Bethesda: NIH; 2017 [cited 2017 Dec 28]. p. 1–5. Available from: https://www.nibib.nih.gov/science-education/science-topics/nuclear-medicine

28. Christensen TE, Bang LE, Holmvang L, Skovgaard DC, Oturai DB, Søholm H, et al. 123I-MIBG Scintigraphy in the Subacute State of Takotsubo Cardiomyopathy. JACC Cardiovasc Imaging [Internet]. 2016 [cited 2017 Dec 1];9(8):982–90. Available from: https://ac.els-cdn.com/S1936878X16302510/1-s2.0-S1936878X16302510-main.pdf?_tid=f57ad1d0-d6be-11e7-9cdd-00000aab0f6c&acdnat=1512150319_a6d943f12f97c2b7e2f9f5c0655cb4c3

29. Perrone-Filardi P, Paolillo S, Dellegrottaglie S, Gargiulo P, Savarese G, Marciano C, et al. Assessment of cardiac sympathetic activity by MIBG imaging in patients with heart failure: A clinical appraisal. Vol. 97, Heart. BMJ Publishing Group Ltd and British Cardiovascular Society; 2011. p. 1828–33.

30. Carrió I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac Sympathetic Imaging With mIBG in Heart Failure [Internet]. Vol. 3, JACC: Cardiovascular Imaging. 2010 [cited 2018 Jan 9]. p. 92–100. Available from: http://imaging.onlinejacc.org/content/jimg/3/1/92.full.pdf

31. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation [Internet]. 2002 [cited 2018 Jan 22];105(4):539–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11815441

32. Chen J. Newer tools for Assessment of Heart Failure. In: Iskandrian AE, editor. Atlas of Nuclear Cardiology. Philadelphia: Elsevier; 2012. p. 341–51.

33. Sestini S, Pestelli F, Leoncini M, Bellandi F, Mazzeo C, Mansi L, et al. The natural history of takotsubo syndrome: a two-year follow-up study with myocardial sympathetic and perfusion G-SPECT imaging. Eur J Nucl Med Mol Imaging [Internet]. 2017 [cited 2017 Nov 23];44(2):267–83. Available from: https://link.springer.com/content/pdf/10.1007%2Fs00259-016-3575-2.pdf

34. Tablas para el cálculo del riesgo coronario a 10 años [Internet]. Girona: REGICOR; 2012 [cited 2017 Dec 20]. Available from: https://www.regicor.org/media/upload/pdf/taules_2012_castella_editora_44_1_1.pdf

35. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, et al. 131I/123I-Metaiodobenzylguanidine (mIBG) scintigraphy: Procedure guidelines for tumour imaging [Internet]. Vol. 37, European Journal of Nuclear Medicine and Molecular Imaging. 2010 [cited 2018 Jan 23]. p. 2436–46. Available from: http://eanm.org/publications/guidelines/gl_onco_mibg_1.pdf

11. ANNEXES

11.1 ANNEX 1: MAYO CLINIC CRITERIA

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma and myocarditis.

11.2 ANNEX 2: INFORMATION SHEET

FULL D'INFORMACIÓ PEL PARTICIPANT [Versió català]

INVESTIGADORS PRINCIPALS: Xavier Albert Bertrán & Sandra Zambrano Gómez.

CODI DEL PROJECTE:

1. **Generalitats del projecte**: El present estudi es durà a terme als departaments de Cardiologia d'11 hospitals de Catalunya en un període de 6 anys i 9 mesos. El projecte d'investigació ha sigut aprovat pel comitè d'ètica d'investigació clínica de cada un dels centres.
2. **Objectius i finalitat de l'estudi**: Amb aquest estudi es pretén determinar la relació entre el patró d'afectació en el moment agut valorat amb SPECT amb ^{123}I-MIBG i el pronòstic clínic a llarg termini, per tal de poder establir un protocol de seguiment diferent en aquells pacients que es demostri un patró d'afectació amb pitjor pronòstic. Per tant, ajudarà a millorar el pronòstic d'aquest tipus de pacients.
3. **Participació**: La seva participació en aquest estudi és totalment voluntària. El participant és lliure de deixar l'estudi si així ho desitja en qualsevol moment, sense necessitat de justificació, i sense que aquesta decisió afecti a la seva assistència sanitària. La participació a l'estudi és totalment gratuïta i no s'obtindrà cap compensació econòmica per la seva participació.
4. **Confidencialitat, protecció de dades i drets del pacient**: s'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la *Ley Orgánica 15/1999* i la informació recollida serà gestionada de forma anònima i només s'utilitzaran amb finalitats d'investigació. També es garanteixen els principis establerts per la *Ley de Investigación biomédica 14/2007* i per la *Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*.
5. **Col·laboració del pacient en la recollida d'informació**: el pacient haurà de firmar el full de participació a l'estudi. 30 dies, 1 any i 3 anys després de l'alta hospitalària se li donarà cita a la qual es recollirà informació sobre vostè i serà afegida a l'estudi. Si per alguna raó ha hagut d'acudir abans a l'hospital o no

acudeix a la cita prèviament concertada, ens posarem en contacte amb vostè per oferir-li una altra data. També se li realitzarà una ecocardiografia als 30 dies, a l'any i als 3 anys i una ressonància magnètica a l'any.

6. **Resultats i benefici de la participació**: El pacient està en el seu dret de ser informat dels resultats de la investigació, així com de no ser informat sobre aquests. Els beneficis derivats de la investigació, poden beneficiar tant al participant com a altres persones, i aquests seran adequadament utilitzats per aconseguir els objectius de l'estudi i serviran de base per futures investigacions en aquest àmbit.

Gràcies per participar.

[En cas necessari, hi ha disponibles versions en altres idiomes]

HOJA DE INFORMACIÓN PARA EL PARTICIPANTE [Versión castellano]

INVESTIGADORES PRINCIPALES: Xavier Albert Bertrán & Sandra Zambrano Gómez.

CÓDIGO DEL PROYECTO:

1. **Generalidades del proyecto**: El presente estudio se llevará a cabo en los departamentos de Cardiología de 11 hospitales de Cataluña en un período de 6 años y 9 meses. El proyecto de investigación ha sido aprobado por el comité de ética de investigación clínica de cada uno de los centros mencionados.
2. **Objetivos y finalidad del estudio**: Con este estudio se pretende determinar la relación entre el patrón de afectación en el momento agudo valorado con SPECT con ^{123}I-MIBG y el pronóstico clínico a largo plazo, con tal de poder establecer un protocolo de seguimiento diferente en esos pacientes que se demuestre un patrón de afectación con peor pronóstico. Por lo tanto, ayudará a mejorar el pronóstico de este tipo de pacientes.
3. **Participación**: Su participación en este estudio es totalmente voluntaria. El participante es libre de dejar el estudio si así lo desea en cualquier momento, sin necesidad de justificación, y sin que esa decisión afecte a su asistencia sanitaria. La participación en el estudio es totalmente gratuita y no se obtendrá ninguna compensación económica por su participación.
4. **Confidencialidad, protección de datos y derechos del paciente**: Se adoptarán las medidas para garantizar la confidencialidad de sus datos en cumplimiento de la *Ley Orgánica 15/1999* y la información recogida será gestionada de forma anónima y solo se utilizarán con fines de investigación. También se garantizarán los principios establecidos por la *Ley de Investigación biomédica 14/2007* y por la *Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*.
5. **Colaboración del paciente en la recogida de información**: el paciente deberá firmar la hoja de participación al estudio. 30 días, 1 año y 3 años después del alta hospitalaria se le dará cita en la cual se recogerá información sobre usted y será añadida al estudio. Si por alguna razón ha tenido que acudir antes al hospital o no acude a la cita previamente concertada, nos pondremos en contacto con

usted para ofrecerle otra fecha. También se le realizará una ecocardiografía a los 30 días, al año y a los 3 años y una resonancia magnética al año.

6. **Resultados y beneficios de la participación**: El paciente está en su derecho de ser informado de los resultados de la investigación, así como de no ser informado acerca de estos. Los beneficios derivados de la investigación, pueden beneficiar al participante como a otras personas, y estos serán adecuadamente utilizados para conseguir los objetivos del estudio y servirán de base para futuras investigaciones en este ámbito.

Gracias por participar.

[En caso necesario, hay disponibles versiones en otros idiomas]

11.3 ANNEX 3: INFORMED CONSENT OF THE STUDY

CONSENTIMENT INFORMAT DE L'ESTUDI

[Versió català]

TÍTOL DE L'ESTUDI: Relationship between iodine – 123 – metaiodobenzylguanidine pattern in the acute phase of Takotsubo syndrome and prognosis: a prospective cohort study.

Jo, Sr/Sra. amb DNI

Afirmo que,

- He rebut i llegit el full d'informació sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte a l'estudi i han sigut respostes de manera satisfactòria.
- He rebut suficient informació sobre les característiques i objectius de l'estudi, els possibles riscos i la importància de la meva contribució per l'avanç de la medicina.
- He estat informat per l'investigador.....de les implicacions i la finalitat de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que les dades facilitades per mi seran totalment confidencials i que seran eliminats del registre un cop finalitzat l'estudi.
- Entenc que puc revocar el meu consentiment informat de participació a l'estudi, sense haver de donar explicacions i sense que això afecti a la meva assistència sanitària.

D'acord amb el que s'ha esmentat anteriorment, accepto voluntàriament la participació a l'estudi.

Dono permís perquè la informació resultant d'aquest estudi sigui utilitzada en futures investigacions relacionades sobre aquesta patologia.

A _____ , a _____ de _____ 20___

Signatura del participant: Signatura de l'investigador:

[En cas necessari, està disponible en altres idiomes]

CONSENTIMIENTO INFORMADO DEL ESTUDIO [Versión castellano]

TÍTULO DEL ESTUDIO: Relationship between iodine – 123 – metaiodobenzylguanidine pattern in the acute phase of Takotsubo syndrome and prognosis: a prospective cohort study.

Yo, Sr/Sra. con DNI

Afirmo que,

- He recibido y leído la hoja de información sobre el estudio que se me ha entregado.
- He podido hacer todas las preguntas necesarias respecto al estudio y han sido respuestas de manera satisfactoria.
- He recibido suficiente información acerca de las características y objetivos del estudio, los posibles riesgos y la importancia de mi contribución para el avance de la medicina.
- He estado informado por el investigador…….de las implicaciones y la finalidad del estudio.
- Entiendo que mi participación es voluntaria.
- Entiendo que los datos facilitados por mi persona serán totalmente confidenciales y que serán eliminados del registro una vez finalizado el estudio.
- Entiendo que puedo revocar mi consentimiento informado de participación en el estudio, sin tener que dar explicaciones y sin que ello afecte a mi asistencia sanitaria.

De acuerdo con lo que se ha mencionado anteriormente, acepto voluntariamente la participación en el estudio.

Doy permiso para que la información resultante de este estudio sea utilizada en futuras investigaciones relacionadas sobre esta patología.

A _____ , a _____ de _____ 20___

Signatura del participant: Signatura de l'investigador:

[En caso necesario, está disponible en otros idiomas]

11.4 ANNEX 4: INFORMED CONSENT OF THE SPECT

Autorització

He estat informat/da sobre l'exploració

____

que el meu metge/ssa m'ha sol·licitat.

He llegit el full informatiu. He estat informat/da sobre les característiques, les alternatives i els possibles riscos generals i específics. També he estat informat/da del dret a acceptar o denegar el procediment, així com del dret a anul·lar l'acceptació realitzada. He entès tot el que se m'ha explicat. Per tot això, dono el meu consentiment per a la pràctica del procediment.

Autorización

He sido informado/a sobre la exploración

____

que mi médico me ha solicitado.

He leído el folleto informativo. He sido informado/a sobre las características de la prueba, las alternativas y los posibles riesgos generales y específicos. También he sido informado/a del derecho a aceptar o denegar el procedimiento así como del derecho a anular la aceptación realizada. He entendido todo lo que se me ha explicado. Por todo ello, doy mi consentimiento a la práctica del procedimiento.

Pacient / Paciente (o responsable legal)

DNI ______________________________

Firma

Testimoni / Testigo

DNI ______________________________

Firma

Persona que informa

Firma ______________________________

Data / Fecha ______________________________

En virtut del disposat en els articles 4,5 i 6 de la Llei Orgànica 15/1999 de 13 de desembre, l'IDI posa en el seu coneixement que disposa d'un fitxer amb dades de caràcter personal denominat FITXER DE PACIENTS de l'IDI. La finalitat de la seva creació és el tractament mèdic-sanitari als usuaris del nostre centre, en la seva totalitat o part del mateix. Els destinataris de la informació són tots els departaments en els quals s'organitza l'IDI així com els estaments oficials públics, privats que per obligació legal o necessitat material hagin d'accedir a les dades a l'efecte de la correcta prestació de l'assistència mèdic-sanitària que constitueix la finalitat del tractament d'aquestes dades. En tot cas, vostè té dret a exercitar els drets d'oposició, accés, rectificació i cancel·lació en l'àmbit reconegut per la Llei Orgànica 15/1999 de 13 de desembre, així com en el Codi Tipus de la Unió Catalana d'Hospitals al que aquest centre està adherit. El responsable del fitxer és l'IDI. Per a exercitar els drets a dalt esmentats, i per a qualsevol aclariment, pot dirigir-se per escrit mitjançant instància dirigida al Responsable del Departament d'informàtica de l'IDI en el següent domicili: Parc Sanitari Pere Virgili. C/ Esteve Terradas, 30. Edifici Mestral, 2a planta, 08023 Barcelona.

En virtud de lo dispuesto en los artículos 4, 5 y 6 de la Ley Orgánica 15/1999 de 13 de diciembre, el IDI pone en su conocimiento que dispone de un fichero con datos de carácter personal denominado FICHERO DE PACIENTES del IDI. La finalidad de su creación es el tratamiento médico-sanitario a los usuarios de nuestro centro, en su totalidad o parte del mismo. Los destinatarios de la información son todos los departamentos en los cuales se organiza el IDI así como los estamentos oficiales públicos, privados que por obligación legal o necesidad material deban acceder a los datos a efectos de la correcta prestación de la asistencia médico-sanitaria que constituye la finalidad del tratamiento de estos datos. En todo caso, usted tiene derecho a ejercitar los derechos de oposición, acceso, rectificación y cancelación en el ámbito reconocido por la Ley Orgánica 15/1999 de 13 de diciembre, así como en el Código Tipo de la Unión Catalana de Hospitales en el que este centro está adherido. El responsable del fichero es el IDI. Para ejercitar los derechos arriba mencionados, y para cualquier aclaración, puede dirigirse por escrito mediante instancia dirigida al Responsable del Departamento de informática del IDI en el siguiente domicilio: Parque Sanitario Pere Virgili. C/ Esteve Terradas, 30. Edificio Mestral, 2ª planta, 08023 Barcelona.

IDI
INSTITUT DE DIAGNÒSTIC PER LA IMATGE

Centre Girona - Unitat MN
Hospital Universitari de Girona
Doctor Josep Trueta
Av. de França, s/n
17007 Girona
Fax 972 20 37 58

Informació i autorització
Información y autorización

MEDICINA NUCLEAR

Centre Girona

Cognoms / Apellidos ______________________________

Nom / Nombre ______________________________

Dia / Día ______________________________

Hora ______________________________

Observacions / Observaciones ______________________________

Consultes i anul·lacions
Consultas y anulaciones

972 22 57 86

Què és la Medicina Nuclear?

És una especialitat mèdica de diagnòstic per la imatge i tractament per mitjà d'un radiofàrmac injectat per via endovenosa.

El radiofàrmac es fixa en un òrgan del cos i permet detectar i analitzar la morfologia i la funció d'aquest a través de la gammacambra.

El temps de duració és molt variable, des de 10 minuts fins a dies sencers, sempre segons el tipus d'exploració, el procediment o l'òrgan per estudiar. Per això pot ser que alguns pacients arribin més tard i entrin abans a la sala d'exploracions.

Què cal tenir en compte?

Abans de la prova

- Si esteu embarassada cal que ho comuniqueu al personal del centre.
- Seguiu el consell del personal del centre.
- Si heu de prendre una medicació específica us citarem uns dies abans per a la prescripció.

Després de la prova

- En la majoria dels casos podeu fer vida normal; en el cas contrari, us informarem de les mesures que haureu de pendre.
- Us farem saber quan podreu recollir els resultats.

¿Qué es la Medicina Nuclear?

Es una especialidad médica de diagnóstico por la imagen y tratamiento por medio de un radiofármaco inyectado por vía endovenosa.

El radiofármaco se fija en un órgano del cuerpo y permite detectar y analizar la morfología y la función de éste a través de la gammacámara.

El tiempo de duración es muy variable, desde 10 minutos hasta días enteros, siempre dependiendo del tipo de exploración, el procedimiento o el órgano a estudiar. Por eso puede ser que algunos pacientes lleguen más tarde y entren antes en la sala de exploraciones.

¿Qué hay que tener en cuenta?

Antes de la prueba

- Si está embarazada es necesario que lo comunique al personal del centro.
- Siga el consejo del personal del centro.
- Si tiene que tomar medicación específica se le citará unos días antes para la prescripción.

Después de la prueba

- En la mayoría de los casos puede hacer vida normal; en caso contrario, le informaremos de las medidas a seguir.
- Se le informará de cuándo puede recoger los resultados.

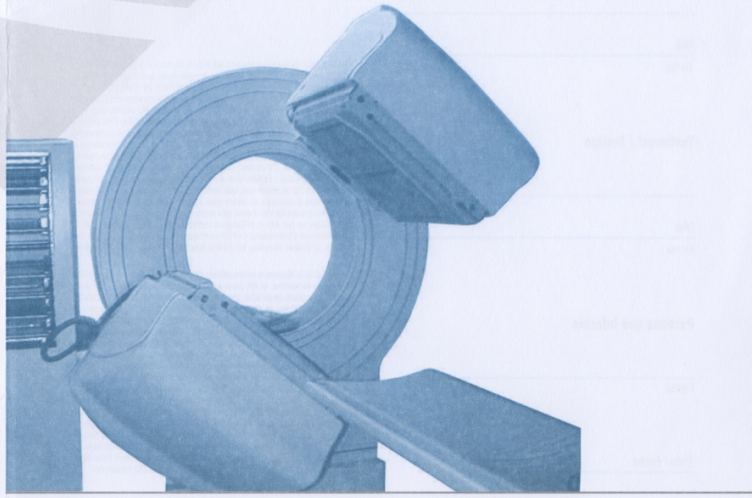
Si esteu embarassada, creieu que podeu estar-ho, o esteu alletant és necessari que ho comuniqueu al personal del centre.

Si teniu qualsevol dubte, poseu-vos en contacte amb el personal de la Unitat de Medicina Nuclear.

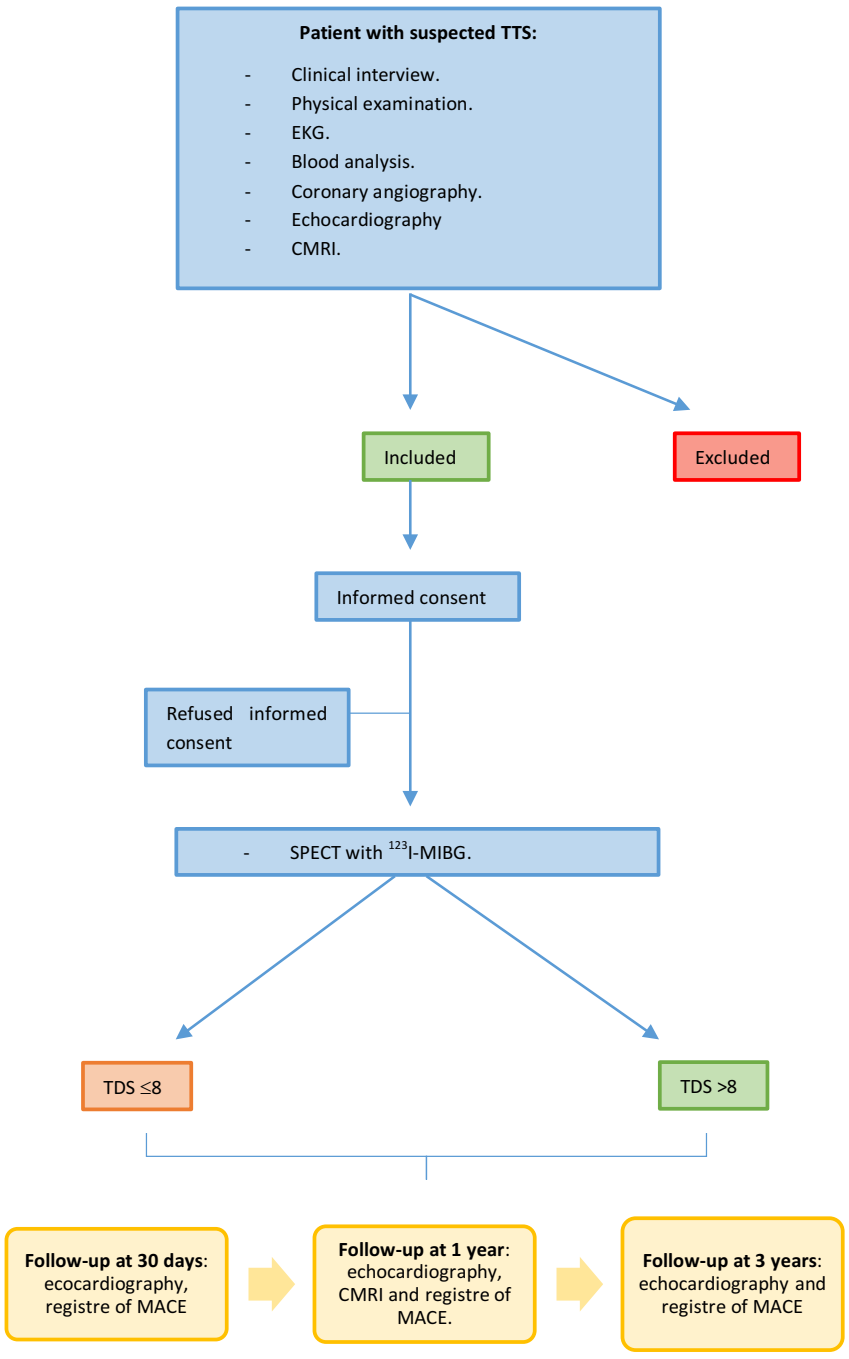
Si está embarazada, cree estarlo o está lactando, es necesario que lo comunique al personal del centro.

Si tiene cualquier duda, póngase en contacto con el personal de la Unidad de Medicina Nuclear.

IDI
INSTITUT DE DIAGNÒSTIC PER LA IMATGE



11.5 ANNEX 5: PATIENT'S FLOW CHART



11.6 ANNEX 6: INFORMATION ABOUT THE PATIENT IN DIAGNOSE

FULL DE DIAGNÒSTIC DEL PACIENT Nº____

- Factors de risc cardiovascular:
  - Edat:
  - Sexe (home/dona):
  - Hipertensió arterial (si/no):
  - Diabetis mellitus (si/no):
  - Dislipèmies (si/no):
  - Fumador (si/no):
- Analítica:
  - HDL (mg/dL):
  - LDL (mg/dL):
  - HbA1c (%):
  - Pic de Troponina-T (ng/dL):
  - CK:
  - CK-MB:
  - NT-proBNP:
- Electrocardiograma (descriure els canvis):
- Ecocardiografia:
  - Fracció d'ejecció del ventricle esquerra (preservada >52%, moderada 52 – 35%, severa <35%):
  - Descriure les alteracions de la motilitat:
  - Altres troballes:
- Desencadenant (físic / emocional / desconegut):
- Coronariografia (descriure troballes):
- Ressonància magnètica amb gadolini (descriure troballes):
- SPECT amb ^{123}I-MIBG:
  - TDS:
  - Severitat (percentatge):
    - Normal (0) =
    - Lleu (1) =
    - Moderat (2) =
    - Sever (3) =
    - Absència (4) =
- Grup:
  - ☐ 1: TDS >8.
  - ☐ 2: TDS ≤8.

Firma del metge responsible (__/__/____):

11.7 ANNEX 7: INFORMATION SHEET AT 30 DAYS

FULL DE SEGUIMENT ALS 30 DIES DEL PACIENT Nº____

- Grup (1 o 2):
- Ecocardiografia:
    - Fracció d'ejecció del ventricle esquerra (preservada >52%, moderada 52 – 35%, severa <35%):
    - Descriure les alteracions de la motilitat:
    - Altres troballes:
- Incidència de MACE als 30 dies (posar el número de successos):
    - Mort per qualsevol causa:
    - Mort per causa cardiovascular:
    - Infart de miocardi:
    - Recurrència de Takotsubo:
    - Reingrés:

Firma del metge (__/__/____):

11.8 ANNEX 8: INFORMATION SHEET AT 1 YEAR

FULL DE SEGUIMENT A L'ANY DEL PACIENT Nº____

- Grup (1 o 2):
- Ecocardiografia:
    - Fracció d'ejecció del ventricle esquerra (preservada >52%, moderada 52 – 35%, severa <35%):
    - Descriure les alteracions de la motilitat:
    - Altres troballes:
- Ressonància magnètica amb gadolini (descriure troballes):
- Incidència de MACE a l'any (posar el número de successos):
    - Mort per qualsevol causa:
    - Mort per causa cardiovascular:
    - Infart de miocardi:
    - Recurrència de Takotsubo:
    - Reingrés:

Firma del metge (__/__/____):

11.9 ANNEX 9: INFORMATION SHEET AT 3 YEARS

FULL DE SEGUIMENT ALS 3 ANYS DEL PACIENT Nº____

- Grup (1 o 2):
- Ecocardiografia:
    - Fracció d'ejecció del ventricle esquerra (preservada >52%, moderada 52 – 35%, severa <35%):
    - Descriure les alteracions de la motilitat:
    - Altres troballes:
- Incidència de MACE als 3 anys (posar el número de successos):
    - Mort per qualsevol causa:
    - Mort per causa cardiovascular:
    - Infart de miocardi:
    - Recurrència de Takotsubo:
    - Reingrés:

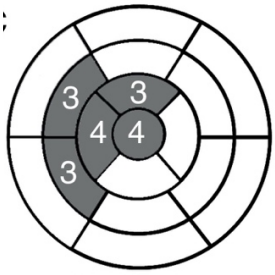
Firma del metge (__/__/____):

11.10 ANNEX 10: DRUGS THAT INTERFERE WITH ^{123}I-MIBG

The following drugs need to be stopped 48h before doing the SPECT with ^{123}I-MIBG.

1. Tricyclic antidepressants:
    - Amitriptyline.
    - Imipramine.
    - Nortriptyline
2. Sympathomimetic.
    - Feliferin.
    - Phenylpropanolamine.
    - Pseudoefrine, ephedrine, methylephedrine
3. Antihypertensive/cardiovascular drugs:
    - Labetalol.
    - Reserpine.
    - Calcium channel blockers.
4. Levodopa.
5. Cocaine.
6. Nordadrenaline.

11.11 ANNEX 11: TDS AND AFFECTION'S SEVERITY CLARIFICATION



In this case, there are 5 segments affected of the total 17 segments of the polar map so this patient has a TDS=5.

The severity of the affection estimated with a percentage will be:

- Normal (0) = 70.6%
- Mildly reduced (1) = 0%
- Moderately reduced (2) = 0%
- Severely reduced (3) = 17.6%
- Absence of uptake (4) = 11.8%