CATCHING BROKEN HEARTS

Electrocardiography and in-hospital outcome in Takotsubo syndrome and ST elevation myocardial infarction

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University of Gothenburg 2022

To Beata, Sigrid and Alfred. ♡
"Family is not an important thing.
It's everything." – Michael J. Fox

Catching broken hearts –
Electrocardiography and in-hospital
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ST elevation myocardial infarction

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A theory is the more impressive the greater the simplicity of its premises is, the more different kinds of things it relates, and the more extended its area of applicability

Albert Einstein, 1949

ABSTRACT

Background and aims: Takotsubo syndrome (TS) and acute myocardial infarction (AMI) have similar symptoms, non-invasive test results and complications. Whereas AMI is caused by cardiac ischemia, the pathophysiology of TS is incompletely understood. Because TS and AMI can present with ST elevation, electrocardiography (ECG) in TS is difficult to distinguish from ST elevation myocardial infarction (STEMI). The aim of this thesis was to compare ECG and outcome between TS and STEMI, and to put these observations into perspective of the pathophysiology of TS.

Methods: All TS patients treated at Sahlgrenska University Hospital (Gothenburg, Sweden) and reported in the Swedish Coronary Angiography and Angioplasty Registry (2008 to 2019) were identified (study I) and matched based on age and sex with STEMI patients (studies II and III). Medical charts, angiography, echocardiography, arrhythmia and ECG were analysed. In study I, the association between T wave inversion and in-hospital Major Adverse Cardiac Events (MACE) was investigated. In study II, life-threatening ventricular arrhythmia (LTVA) or death within 72 hours was investigated in TS versus STEMI. In study III, admission ECG, and ECG predictors of LTVA or death, were compared between ST elevation Takotsubo syndrome (STE-TS) and STEMI. In study IV, TS and anterior STEMI patients were prospectively enrolled to validate the results in study III, and to analyse temporal ECG.

Results: The risk of LTVA within 72 hours was lower in TS than in STEMI (study II, N=465). ST deviation magnitude predicted ***higher*** risk

of LTVA or death within 72 hours in STEMI (study III, N=378), whereas T wave inversion predicted ***lower*** risk of in-hospital MACE in TS (study I, N=215). In study III, admission ECG was similar in STE-TS and left anterior descending artery (LAD) STEMI. In temporal analysis (study IV, N=130), the similarities between TS and anterior/LAD STEMI from study III were confirmed, and similarities of T wave inversion were emphasized.

Conclusions: The risk of LTVA within 72 hours was lower in TS than in STEMI. Admission/temporal ECG was similar, but ECG predictors of outcome were different, in TS compared with anterior/LAD STEMI. This thesis indicate that ECG cannot safely distinguish TS from STEMI. Lastly, the observations of the present thesis may indicate a "transient ischemic" pathophysiology of TS.

Keywords: Takotsubo syndrome, ST elevation myocardial infarction, electrocardiography, arrhythmia, mortality, pathophysiology.

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Hjärtsjukdomen Takotsubo, i populärvetenskapliga sammanhang kallad ”brustet hjärta”, kännetecknas av en plötsligt uppkommen, svårt nedsatt pumpförmåga hos hjärtat (akut hjärtsvikt). Takotsubo uppkommer vanligtvis efter kraftig känslomässig eller fysisk stress, och 90 % av patienterna är kvinnor i åldrarna efter menopaus (medelålder vid insjuknande 67–70 år). Symptom och akuta tecken vid Takotsubo liknar dem som kännetecknar hjärtinfarkt. Elektrokardiografi (EKG, hörnstenen för tidig diagnostik av akuta hjärtsjukdomar) visar ofta en liknande bild vid båda sjukdomarna. Den huvudsakliga skillnaden är att patienter med Takotsubo inte drabbas av någon bestående hjärtskada, och att pumpförmågan spontant återhämtar sig inom dagar till veckor, utan behandling i typfallet (även om komplikationer, även dödliga, kan tillstöta). Vid hjärtinfarkt kan skada på hjärtmuskeln leda till bestående nedsatt pumpförmåga (kronisk hjärtsvikt) även vid optimal behandling. Hjärtinfarkt orsakas oftast av en blodpropp i hjärtats kranskärl, som i sin tur leder till att hjärtats egen blodförsörjning hindras, och att syrebrist i hjärtmuskeln uppstår. Orsaken till Takotsubo är däremot inte klarlagd, även om kraftig frisättning av kroppens egna stress-ämnen (såsom adrenalin och noradrenalin) tros spela en central roll.

Syfte: Syftet med denna avhandling var att jämföra EKG, allvarliga hjärtrytm-rubbningar och dödlighet mellan Takotsubo och hjärtinfarkt, samt att försöka koppla dessa observationer till en möjlig orsak till Takotsubo.

Metoder: Granskning genomfördes av alla 215 patienter som vårdades för Takotsubo på Sahlgrenska Universitetssjukhuset (Göteborg, Sverige) mellan år 2008 och 2019 (delarbete 1). Granskning genomfördes även av de 596 patienter med samma ålder och kön som vårdades för den allvarligaste formen av hjärtinfarkt (hjärtinfarkt med ST-höjning på EKG, så kallad ”ST-höjningsinfarkt”) under samma tidsperiod (delarbete 2 och 3). I samtliga delarbeten (1–4) analyserades patientjournaler och EKG; samt specifika journal-rapporter om hjärtrytm-rubbningar, hjärt-ultraljud och kranskärls-röntgen. I delarbete 1 undersöktes om EKG vid ankomst till sjukhus för Takotsubo kunde förutsäga prognos under sjukhusvistelsen. I delarbete 2 jämfördes prognos (allvarliga hjärtrytm-rubbningar eller död) vid Takotsubo respektive ST-höjningsinfarkt. För att undersöka om EKG vid ankomst till sjukhus kunde skilja Takotsubo från ST-höjningsinfarkt, jämfördes Takotsubo-patienter med ST-höjning på EKG gentemot patienter med ST-höjningsinfarkt, i delarbete 3. I delarbete 4 rekryterades nya patienter (29 med Takotsubo [alla kvinnor], 101 med ST-höjningsinfarkt), prospektivt (följdes från insjuknande jämfört med i efterhand som i delarbete 1–3) för att befästa EKG-fynden från delarbete 3, samt för att jämföra EKG över tid mellan Takotsubo och ST-höjningsinfarkt.

Resultat: Risken för allvarliga hjärtrytm-rubbningar eller död (inom 72 timmar från ankomst) var betydligt lägre vid Takotsubo jämfört med ST-höjningsinfarkt (delarbete 2). EKG vid ankomst till sjukhus var mycket likt vid Takotsubo och ST-höjningsinfarkt, förutsatt att den senare enbart drabbade hjärtats framvägg (delarbete 3). Vid jämförelse av EKG från sjukhusankomst till dag 30 efter ankomst, påvisades samma likheter (delarbete 3 och 4), men till exempel ST-höjning var mindre vanligt i Takotsubo än ST-höjningsinfarkt i hjärtats framvägg. Förändringar i ”T-vågen” på EKG visade sig däremot vara mer likt mellan sjukdomsgrupperna jämfört med vad som har rapporterats i tidig-

are forskning. I en särskild analys av de patienter (9 med Takotsubo, 43 med ST-höjningsinfarkt) som undersöktes med EKG inom 60 minuter från första symtom syntes inga EKG-skillnader mellan Takotsubo eller ST-höjningsinfarkt i hjärtats framvägg. Att förekomsten av ST-höjning då var lika vanligt i vid båda sjukdomarna kan ha betydelse för de sjukdomsalstrande orsakerna till Takotsubo, eftersom ST-höjning i sig kan tyda på syrebrist genom hela hjärtats muskelvägg. Därför kan denna likhet teoretiskt tyda på att Takotsubo-patienterna hade syrebrist i hjärtats muskelvägg tidigt i förloppet, men att denna tid hypotetiskt var för kort för att orsaka skada. Slutligen kunde förändringar i T-vågen på ankomst-EKG förutsäga ***lägre*** risk för allvarliga hjärt-komplikationer (under hela sjukhusvistelsen) i Takotsubo (delarbete 1), medan förändringar i ”ST-sträckan” på EKG kunder förutsäga ***högre*** risk för dålig prognos (inom 72 timmar) hos patienter med ST-höjningsinfarkt (delarbete 3).

Slutsats: Risken för allvarliga hjärtrytm-rubbningar eller död inom 72 timmar från ankomst till sjukhus var betydligt lägre hos patienter med Takotsubo jämfört med ST-höjningsinfarkt. EKG var mycket likt vid Takotsubo jämfört med ST-höjningsinfarkt i hjärtats framvägg, där EKG-förändringar i T-vågen kunde förutsäga ***bättre*** prognos vid Takotsubo, medan EKG-förändringar i ST-sträckan kunde förutsäga ***sämre*** prognos vid ST-höjningsinfarkt. Även om orsaken till Takotsubo inte undersöktes specifikt i denna avhandling, så kan observationerna från delarbete 2–4 indirekt kopplas till övergående syrebrist i hjärtat som en teoretisk sjukdomsalstrande orsak. Slutligen är det av stor vikt att skilja Takotsubo från hjärtinfarkt, eftersom patienter med Takotsubo kan ta skada av medicinsk behandling för hjärtinfarkt, och på grund av risken med att missa att behandla en hjärtinfarkt. Med hänsyn till detta visade denna avhandling inga förutsättningar för att använda EKG som ett diagnostiskt verktyg för att skilja Takotsubo från hjärtinfarkt.

LIST OF STUDIES

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Jha S, Zeijlon R, Enabtawi I, Shekka Espinosa A, Chamat J, Omerovic E, Redfors B. Electrocardiographic predictors of adverse in-hospital outcomes in the Takotsubo syndrome. *Int J Cardiol* 2020; 299: 43-18.

II. Zeijlon R, Chamat J, Enabtawi I, Jha S, Mohammed MM, Wågerman J, Le V, Shekka Espinosa A, Nyman E, Omerovic E, Redfors B. Risk of in-hospital life-threatening ventricular arrhythmia or death after ST-elevation myocardial infarction versus the Takotsubo syndrome. *ESC Heart Failure* 2021; 8: 1314-1323.

III. Zeijlon R, Chamat J, Le V, Wågerman J, Enabtawi I, Jha S, Mohammed MM, Shekka Espinosa A, Angerås O, Råmunddal T, Omerovic E, Redfors B. ECG differences and ECG predictors in patients presenting with ST segment elevation due to myocardial infarction versus takotsubo syndrome. *IJC Heart & Vasculature* 2022; 40: 101047.

IV. Zeijlon R, Jha S, Le V, Chamat J, Shekka Espinosa A, Poller A, James Thorleifsson S, Bobbio E, Mellberg T, Pirazzi C, Gudmundsson T, Martinsson A, Angerås O, Råmunddal T, Omerovic E, Redfors B. Temporal electrocardiographic changes in anterior ST elevation myocardial infarction versus the Takotsubo syndrome. *Submitted to journal.*

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ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndrome
AHF	Acute heart failure
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
ARB	Aldosterone receptor blockers
ATP	Adenosine triphosphate
BMI	Body mass index
CABG	Coronary artery bypass graft
CFR	Coronary flow reserve
CMR	Cardiac magnetic resonance imaging
cTn	cardiac Troponin
DAPT	Dual anti-platelet therapy
ECG	Electrocardiography
eCRF	Electronical case report form
ESC	European Society of Cardiology
I/R	Ischemia-reperfusion
IDH	Ischemic heart disease
IQR	Interquartile range
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LCx	Left circumflex artery
LTA	Life-threatening arrhythmia
LTVA	Life-threatening ventricular arrhythmia
LV	Left ventricular
LVOTO	Left-ventricular outflow tract obstruction
MACE	Major Adverse Cardiac Events

MI	Myocardial infarction
N	Total number
NA	Not applicable
NSTEMI	Non-ST elevation myocardial infarction
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-terminal-pro hormone BNP
OR	Odds ratio
PCI	Percutaneous coronary intervention
pro-BNP	pro hormone BNP
PS	Propensity score
QTc	Corrected QT time
RCA	Right coronary artery
ROS	Reactive oxygen species
RV	Right ventricular
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SPECT	Single-photon emission computed tomography
STAMI	Stunning in Takotsubo and Acute Myocardial Infarction
STEMI	ST elevation myocardial infarction
STE-TS	ST elevation Takotsubo syndrome
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
TS	Takotsubo syndrome
U.S.	United States
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1

INTRODUCTION

"The possession of knowledge does not kill the sense of wonder and mystery. There is always more mystery."

Anaïs Nin

1.1

THE TAKOTSUBO SYNDROME

The Takotsubo syndrome was first described in a Japanese medical textbook in 1990 – "*Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm*" and a case series of the first five patients were published in 1991 [1, 2]. The distinctive feature of this acute heart failure syndrome is its close association with emotional or physical stress as "trigger". The name "Takotsubo" stems from the typical shape of the hearts' left ventricle in TS, closely resembling a Japanese octopus trap (tako = octopus; tsubo = pot, Figure 1) [3]. According to previous literature, the condition has acquired 75 different names, where the more frequently used are "apical ballooning syndrome", "transient apical ballooning", "stress-induced cardiomyopathy" and "Takotsubo cardiomyopathy" [3]. In patient information, and in popular science, the condition is generally called "Broken heart syndrome" [4]. Although the term *Takotsubo cardiomyopathy* has been suggested as the official term [3], this may imply a more persistent condition (as with other cardiomyopathies) than the transient nature of Takotsubo. Furthermore, there are similarities between Takotsubo and *Acute Coronary Syndrome*

(ACS). Therefore (although there is no complete agreement regarding the nomenclature), the term *Takotsubo syndrome* (TS) has been proposed as a the most suitable term [5].

Figure 1. Tako-tsubo. Octopus trap with octopus.

1.1.1 EPIDEMIOLOGY

The exact incidence of TS is not known, however, in a large United States (U.S.) cohort the incidence was around 15 to 30 cases per 100 000 per year, with similar numbers reported in Europe [6]. It has been estimated that TS account for approximately 1-2% of all patients with suspected ACS, and for 5-6% (Figure 2) of all female patients presenting with suspected ST elevation myocardial infarction (STEMI) [5, 7]. TS predominately affect women and around 90% of patients are women after menopause (mean age 67-70 years) [5]. Compared with men in the same age, cardiac disease in general is less common in premenopausal women, which has been attributed to cardioprotective effects of oestrogen [8]. Decreasing estrogenic levels with age in women

is a possible explanation for the female pre-dominance in TS (covered in greater detail under section 1.3.1) [9]. Male patients with TS have a higher prevalence of physical triggers in relation to emotional triggers, and a higher mortality compared with female patients. Although these differences between men and women with TS are not clearly understood, the physical triggers per se probably contribute to the higher mortality observed in men [9, 10].

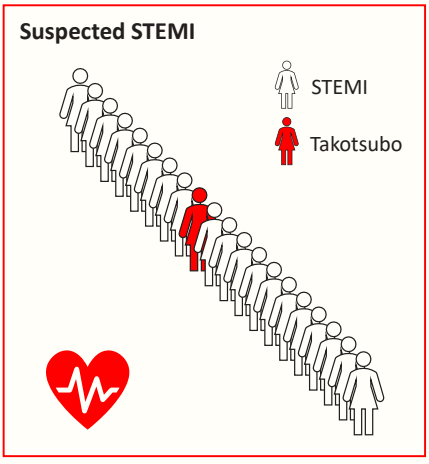


Figure 2. Epidemiology of Takotsubo syndrome. Takotsubo syndrome accounts for approximately 1 of 20 cases (5-6%) with suspected STEMI among women. STEMI = ST elevation myocardial infarction.

1.1.2 SIGNS AND SYMPTOMS

TS is associated with severe emotional or physical stress ("trigger") and is characterized by rapid onset of left ventricular dysfunction, typically in the apical region of the heart. Admission electrocardiography (ECG) typically display ST elevation and/or T wave inversion (covered in greater detail under section 1.3.2) [5, 7, 11]. The cardiac dysfunction is transient and resolves spontaneously within days to weeks for most patients [7].

Despite the initial severity of left ventricular dysfunction, the patient is typically relatively hemodynamically compensated. That is, the clinical magnitude of acute heart failure in TS does not correspond to that caused by other types of heart disease (e.g. acute myocardial infarction), with the corresponding severity of left ventricular dysfunction [12, 13]. However, some patients develop cardiogenic shock and/or experience complications such as pulmonary oedema or arrhythmia, which may be fatal [14].

TS is divided into 1) *Primary* TS, when the cardiac symptoms are the reason for seeking health care (in general emotional or no trigger), and 2) *Secondary* TS, when TS develops in a patient receiving health care for another condition (in general physical trigger) [7]. The most common symptoms of primary TS are dyspnoea, chest pain and/or syncope; but the presenting symptoms of TS may differ depending on the underlying trigger. In secondary TS, the same symptoms may develop, but these symptoms may be masked by an underlying illness; such as stroke, seizures, hemodynamic instability or impaired consciousness [5, 15].

In addition to the different triggers of TS, there are different phenotypes of TS depending on the regionality of wall-motion abnormality. *Typical TS* is the *apical type*, with apical and/or apical and midventricular hypokinesia and basal hypercontractility, accounting for approximately 80% of cases. All other types of TS are defined as *atypical TS*. The *midventricular type* (midventricular hypokinesia and both apical and basal hypercontractility) accounts for around 15% of cases, and the remaining cases are of the *inverse/basal type* (basal hypokinesia and apical hypercontractility) or the *focal type* (focal hypokinesia not corresponding to any of the other types). In rare cases, right ventricular or biventricular TS has been reported. [5, 7, 16]

1.1.3 PATHOPHYSIOLOGY

Catecholamine excess

There is near agreement that intense sympathetic stimulation leading to catecholamine excess (primarily through excessive release of epinephrine and norepinephrine) plays a central role in the pathophysiology of TS [5]. Indeed, in approximately 3 of 4 cases of TS, an emotional or physical trigger can be identified [11]. In patients with TS, increased blood flow has been observed in anatomical regions of the brain involved in stress response (hippocampus, brainstem and basal ganglia). In response to stress in general, brainstem noradrenergic neurons and sympathetic adrenomedullary circuits are activated, leading to secretion of catecholamines (Figure 3) [17].

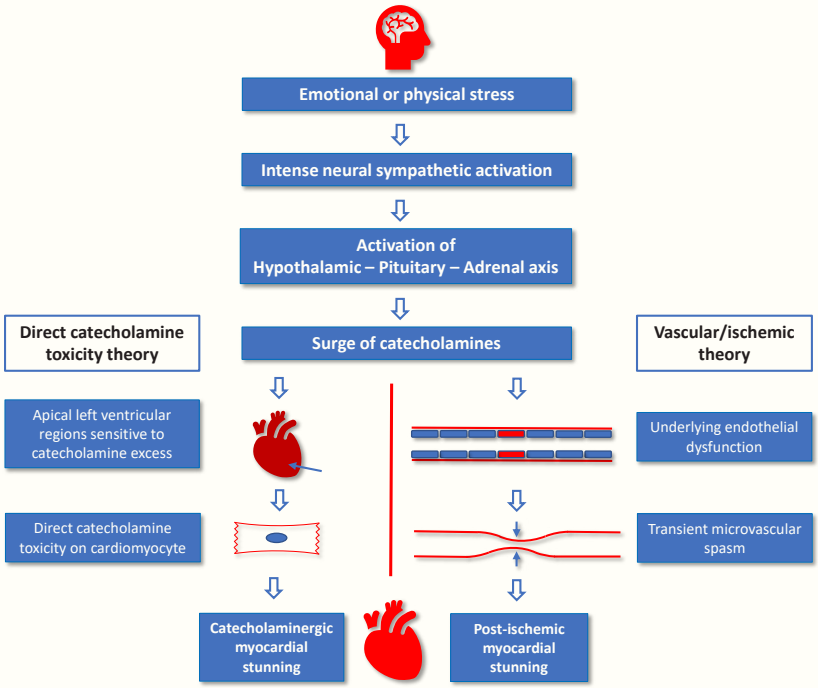


Figure 3. Theories of the pathophysiology of Takotsubo syndrome.

Downstream of the central nervous system, previous research on TS has shown high levels of norepinephrine in the coronary sinus and elevated levels of catecholamines (epinephrine, norepinephrine, dopamine) in plasma [5, 7, 17]. In addition, exogenous administration of inotropic synthetic catecholaminergic drugs (dobutamine infusion in routine diagnostic stress testing for suspected coronary artery disease) has induced TS in several reported cases [18, 19]. Also, TS has been induced in animal experiments through intravenous administration of catecholaminergic drugs [5, 20].

At the cardiac level, most previous research and theories point towards myocardial stunning as the explanation for the mechanical dysfunction per se. However, there are different theories regarding the pathophysiological link between catecholamine excess and myocardial stunning. [5, 17, 21, 22]

Myocardial stunning

The term "stunned myocardium" was coined in 1982 as an explanation for prolonged, but reversible, ventricular dysfunction after transient periods of myocardial ischemia [23]. The associated term "hibernating myocardium" describes another state of reduced myocardial function, probably caused by the same pathophysiologic mechanisms. While the contractile dysfunction seen in myocardial stunning is per definition *after* restoration of myocardial perfusion, hibernating myocardium is contractile dysfunction under circumstances with reduced perfusion. In both situations, the stunned and hibernating myocardium is viable with potential to regain contractile function [24].

In animal models, myocardial stunning was induced by short period of ischemia, where the duration of myocardial dysfunction was dependent on the duration of ischemia. Coronary occlusion in dogs for 5 and 15 minutes led to contractile dysfunction with full recovery after 4 and

24 hours respectively. ST elevation (when present) resolved within one minute and left ventricular pressure recovered within 15 minutes [25, 26]. Several later studies replicated similar results [25-28]. The most important cellular mechanisms in myocardial stunning are increase of reactive oxygen species (ROS) and alterations in excitation-contraction coupling, with reduced responsiveness to calcium in the cardiomyocyte contractile apparatus [25].

Link between catecholamine excess and myocardial stunning

Several theories regarding the link between catecholamine excess and myocardial stunning has emerged over time [5, 17, 21, 29]. In the present thesis, the two main theories will be divided into the following: 1) The direct catecholamine toxicity theory and 2) The vascular/ischemic theory. Many authors lean towards one or the other theory, where the catecholamine toxicity theory has been amplified in recent years [5, 21], but a combination of both mechanisms has also been suggested [17, 21].

Direct catecholamine toxicity theory

The histopathological finding of contraction band necrosis in endomyocardial biopsies from TS patients has been proposed as possible evidence for direct catecholamine toxicity in TS [30]. Contraction band necrosis is also seen in other conditions with catecholamine excess (pheochromocytoma, subarachnoid haemorrhage), which serves as the link between this histopathological finding and possible direct catecholamine toxicity in TS [5, 21, 30].

The direct catecholamine toxicity theory stipulates that catecholamine excess can induce cardiomyocyte dysfunction through intense activation (through epinephrine specifically) of beta-2-adrenergic receptors leading to a "molecular switch" from the positive inotropic G_S protein pathway to the negative inotropic G_i protein pathway. In the left ventricle of the healthy heart in all studied mammals (in humans not studied/

not known), the highest density of beta-1- and beta-2-adrenergic receptors are found in the apex. Conversely, the sympathetic innervation in the left ventricle of the human heart is lowest in the apex and highest in the basal regions. With reference to the distribution of receptor density and the innervation of the left ventricle, the apical regions may be most sensitive to catecholamines excessively secreted from adrenal glands, which could possibly explain the typical apical hypokinesia seen in TS [5, 17, 21, 30]. However, this does not explain the different phenotypes of TS (midventricular, basal, focal), where theories regarding regional re-distribution of beta-adrenergic receptors because of recurrent TS episodes has been put forward to expand the theory to all phenotypes [21].

Furthermore, there is a theory that the cardiomyocytes response to catecholamine toxicity is part of a protective mechanism. According to this theory, the "molecular switch" from positive inotropic G_s signalling to negative inotropic G_i signalling could decrease the metabolic demand on the cardiomyocyte. This, in combination with anti-apoptotic mechanisms (by the phosphoinositide 3-kinase/protein kinase B (AKT) survival pathway) could limit the acute myocardial injury in response to catecholamine excess [5].

Vascular/ischemic theory

In their first description of TS, Sato et al suggested multivessel coronary spasm as the pathophysiological cause [1]. This was based on theoretical reasoning and the fact that epicardial spasm was observed in four of the five first described cases of TS [1, 2]. In a later study, vasospasm was investigated through intracoronary administration of the coronary vasoconstrictor acetylcholine in 48 of 88 patients, whereof 21% (10/48) demonstrated coronary spasm [31]. In a study from 2008,

typical TS was provoked in one of four patients after intracoronary acetylcholine [32].

An extension of the vascular/ischemic theory is the theory of microvascular dysfunction and/or microvascular spasm, where coronary/epicardial spasm may not be observable [33]. Under circumstances of catecholamine excess, an underlying coronary microvascular dysfunction; including endothelial dysfunction; may lead to intense microvascular constriction and post-ischemic myocardial stunning [17, 33]. When comparing patients with TS or STEMI, evidence of acute and reversible microvascular vasoconstriction was found in TS but not in STEMI; and all patients in the TS group showed a perfusion defect in the area of cardiac dysfunction [34]. Another study of coronary flow reserve (CFR) in TS demonstrated a profound, diffuse, reversible coronary microcirculatory disturbance in the acute phase [35]. Several other studies, e.g. through SPECT (single-photon emission computed tomography), have found signs of microcirculatory dysfunction in TS [17].

Under normal circumstances, the response of epicardial arteries and coronary micro-vessels to sympathetic stimulation is vasodilatation, through activation of beta-2-receptors. Vasoconstriction is primarily mediated by alpha-1-receptors in larger coronary arteries, and alpha-2-receptors in the microcirculation. In normal coronary circulation, intact endothelium opposes this alpha-adrenergic vasoconstriction, with normal myocardial perfusion despite intense sympathetic stimulation. However, in the setting of endothelial dysfunction; and/or exhaustion of autoregulation; alpha-adrenergic vasoconstriction becomes unrestrained and powerful enough to reduce coronary blood flow and cause myocardial ischemia [36]. In this setting, both alpha-1- and alpha-2-adrenoreceptors can mediate constriction of the microcirculation, leading to ischemia and limitation of myocardial function [17, 36]. Indeed, impaired peripheral endothelium-dependent vasodi-

lation and microvascular constriction has been observed in patients with TS [37]. Furthermore, endothelial dysfunction is age-related and related to estrogenic deficiency, which could explain the predominance of postmenopausal women in TS [17].

1.1.4 DIAGNOSIS

TS is classified as myocardial injury but not as myocardial infarction, according to the Fourth Universal Definition of Myocardial Infarction [38]. The diagnostic criteria for TS according to the European Society of Cardiology (ESC) are presented in table 1 [7].

Table 1. Diagnostic criteria of Takotsubo syndrome[1]

Transient regional wall motion abnormalities of the left ventricular (LV) or right ventricular (RV) myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
The regional wall motion abnormalities usually[a] extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).
New and reversible electrocardiography (ECG) abnormalities (ST-segment elevation, ST depression, LBBB[b], T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).

[1] 7. 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. Eur J Heart Fail. 2016;18(1):8-27.

Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present).[c]
Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).[d]

a. Acute, reversible dysfunction of a single coronary territory has been reported.
b. Left bundle branch block may be permanent after Takotsubo syndrome, but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take many weeks to months to normalize after recovery of LV function.
c. Troponin-negative cases have been reported, but are atypical.
d. Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed.

1.1.5 TREATMENT

Because of the lack of prospective randomized clinical trials there are no guideline- or evidence-based treatments for TS. Of note, a large prospective randomized clinical trial (BROKEN SWEDEHEART) of adenosine for treating TS is currently being conducted at Sahlgrenska University Hospital (Gothenburg, Sweden). However, the current treatment for TS is based on observational studies, meta-analyses, case series and expert consensus [14]. Because of the close similarities between TS and ACS, the pre-hospital; and initial in-hospital; treatment should follow guidelines of ACS (in patients with ACS symptoms, covered below in section 1.2.3) [7, 14]. Since TS is reversible without specific treatment, the overall management should focus on avoiding unnecessary (potentially harmful) treatment; and treating complications, such as pulmonary oedema, arrhythmia or cardiogenic shock [6, 7, 14, 15].

When the TS diagnosis is established, patients should be evaluated for the presence of left-ventricular outflow tract obstruction (LVOTO). If LVOTO is not present, fluid resuscitation is the main treatment for hemodynamic instability. If LVOTO is present, short-acting beta-blockers (e.g. esmolol or landiolol) may be used if fluid resuscitation is not sufficient [15]. Another treatment option for TS patients with LVOTO may be the calcium sensitizer levosimendan (as an alternative to inotropic drugs) or the If-channel inhibitor Ivabradine, which lowers heart rate without reducing contractility (although data is lacking for this treatment in TS) [14, 15]. Inotropic drugs should not be used, since this can exaggerate LVOTO [6, 15]. Also, inotropic drugs may have a negative impact on prognosis in TS overall, based on higher mortality observed in TS patients treated with inotropes as well as catecholaminergic excess as part of the pathophysiological cause of TS [7, 14]. Of note, patients with secondary TS (especially the critically ill) are less tolerant to TS. If these patients should deteriorate hemodynamically, vasoactive treatment should be discontinued and mechanical assist device should be considered [6, 15].

Until recovery of left ventricular dysfunction, beta-blocker treatment may be reasonable although evidence is lacking. Angiotensin converting enzyme inhibitors (ACEi) or aldosterone receptor blockers (ARB) may facilitate recovery of left ventricular function and diuretics should be administered to patients with signs of interstitial fluid/pulmonary oedema. There should be caution with QT prolonging drugs, and anticoagulation should be given to patients with left ventricular ejection fraction <20% to avoid thromboembolic events. ACEi/ARB may improve long term survival but there is no evidence for long term treatment with beta-blockers. Aspirin and statins are appropriate if concomitant atherosclerosis in present at diagnostic work-up. [7, 14, 15].

1.2

ACUTE MYOCARDIAL INFARCTION

The history of acute myocardial infarction (AMI) dates back much longer than that of TS. William Harvey, the first known physician to comprehensively describe that blood circulates [39], described the first cases suggesting AMI in the 17th century (Figure 4). Although the pathogenesis was unknown, the first description of angina pectoris by a medical person was by William Heberden in 1768 [40]. The initial recognition of AMI is attributed to George Dock, in his 1896 paper "Notes on the coronary arteries" [41, 42]. Ludwing Hektoen broadened the concept further in 1899 by suggesting both embolism and thrombosis can cause AMI, and by describing the cause as "sclerotic changes in the coronaries" [42]. From being fatal in the vast majority of cases in the early 20th century, through the era of fibrinolysis in the 1970s and 80s, to today's percutaneous coronary intervention (PCI) era, the treatment of AMI is one of the great triumphs of medicine [42, 43].

Figure 4. Doctor William Harvey 1627. The first known physician to report cases of acute myocardial infarction and describe the systemic blood circulation in detail. Link to original: https://en.wikipedia.org/wiki/William_Harvey . Used in accordance with CC BY 4.0: https://creativecommons.org/licences/by/4.0/

1.2.1 EPIDEMIOLOGY

Worldwide, ischemic heart disease (IHD) is the most common cause of death [44]. The incidence rate for STEMI is decreasing while the incidence rate for non-ST elevation myocardial infarction (NSTEMI) is increasing [44, 45]. In women, IHD develops on average 7-10 years later than in men [44]; and in patients <60 years old, STEMI in less common in women compared with men [46]. The incidence of STEMI was 58 per 100 000 per year in 2015, according to the largest registry in Europe, SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies). The incidence in the U.S. is similar with 50 cases of STEMI per 100 000 per year in 2008, where STEMI constitute 25 to 40% of all AMI cases. [44, 45].

1.2.2 SYMPTOMS, DIAGNOSIS AND PATHOPHYSIOLOGY

Symptoms

Although symptoms are sometimes diffuse (such as palpitations, nausea, syncope or no symptoms), classical symptoms of myocardial ischemia include chest pain/discomfort; upper extremity and/or mandibular pain; or dyspnoea, either at rest or during exertion [38, 44]. Patients with AMI (especially STEMI), may also present with cardiac arrest due VF or other malignant arrythmias, which is a common cause of death in STEMI. Cardiac arrest and sudden cardiac death due to STEMI primarily occur pre-hospital [44]. The diagnosis of different types of MI are based on electrocardiography as well as the underlying pathological cause, however, the definitions of myocardial injury or infarction are equivalent irrespective of cause [38].

Diagnostic definitions

The criterion for *myocardial injury* is detection of an elevated cTn value above the 99th percentile upper reference limit. This injury is considered *acute* if there is a rise and/or fall of cTn values. In turn, myocardial *infarction* (MI) is defined as *the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia*. Evidence of myocardial ischemia is considered as clinical symptoms and/or ECG changes associated with ischemia. It is important to note that non-ischemic myocardial injury could arise from e.g. myocarditis, or non-cardiac condition such as renal failure. [38, 44].

MI and unstable angina fall under the umbrella term ACS. MI is further sub-categorized according to whether or not the patient has persistent ST elevation on ECG, as ST elevation or non-ST elevation myocardial infarction. These categories are important for the immediate treatment strategies, which are also affected by the underlying pathophysiological cause of MI [44, 47].

Pathophysiology

From the pathophysiological perspective, myocardial ischemia results from imbalance between myocardial oxygen supply and demand. *Infarction* of the myocardium is pathologically defined as myocardial cell death duo to prolonged ischemia, where necrosis progresses from the inner sub-endocardium to the outer sub-epicardium (Figure 5) [38]. The reasons for the higher vulnerability to ischemia of the sub-endocardium is not completely understood. However, possible explanations include increased systolic sub-endocardial vessel resistance, transient sub-endocardial vessel collapse or higher compliance of sub-endocardial vasculature [48]. In humans, ischemia can persist for hours before myocardial necrosis occurs, because of collateral blood flow, reduced demand, or preconditioning through intermittent occlusion [38]. Of

note, even very brief episodes of ischemia; too short to cause necrosis; can cause elevations of cardiac Troponin (cTn) [38].

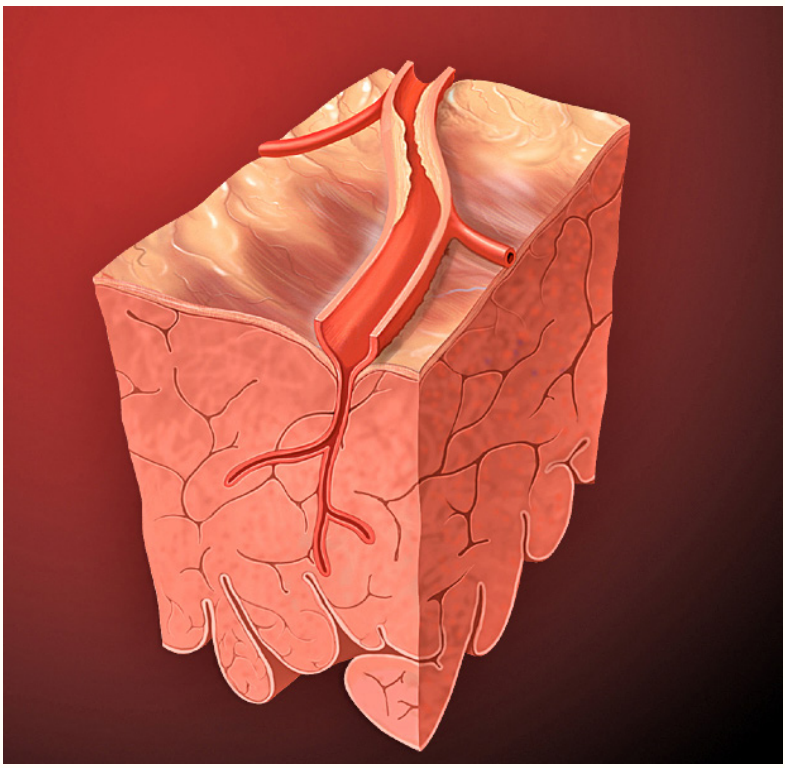


Figure 5. Myocardial wall. Illustration of the outer myocardial wall (epicardium, top of picture) with sub-occluded epicardial artery and vessels extending towards the inner myocardial wall (endocardium, bottom of picture). Link to original https://mriquestions.com/perfusion-why-and-how.html Used in accordance with CC BY 4.0: https://creativecommons.org/licences/by/4.0/

Types of myocardial infarction

In addition to the categories STEMI and NSTEMI, MI is divided into five main types according to pathogenesis [38, 44, 47]:

- **Type I**
  MI caused by acute coronary atherothrombotic myocardial injury due to plaque rupture/erosion and associated thrombosis.

- **Type II**
  MI caused by oxygen supply-demand mismatch, i.e. the supply of oxygen to the myocardium does not meet the demand (due to reasons such as e.g. severe anaemia, low blood pressure or coronary artery spasm).

- **Type III**
  Sudden unexpected cardiac death where the symptoms and/or autopsy results suggest MI.

- **Type IV a-c**
  MI associated with the PCI-procedure (a), in-stent thrombosis (b) or re-stenosis after PCI (c).

- **Type V**
  MI associated with coronary artery bypass graft (CABG) surgery.

Among the types of MI, only type I STEMI, will be covered in the present thesis.

Myocardial infarction with persistent ST elevation

According to ECG, STEMI is defined as persistent (> 20 minutes) ST segment elevation in at least two contiguous leads with the following lead-specific cut-offs: ST segment elevation ≥ 2 mm in men ≥ 40 years

old, ≥ 2.5 mm in men < 40 years old or ≥ 1.5 mm in women, in leads V2-V3; or ≥ 1 mm ST segment elevation in the remaining leads. ST segment depression in V1-V3 with ST segment elevation ≥ 0.5 mm in additional leads V7-V9 indicate posterior MI. These ECG patterns indicate ongoing coronary artery occlusion (Figure 6) [44]. Of note, hyperacute T waves with ST depression may precede ST elevation in STEMI [45]. Most cases of STEMI are categorized as type I MI, caused by coronary epicardial artery obstruction. This obstruction is generally secondary to atherosclerotic plaque disruption with thrombus formation, with myocardial infarction/stunning and wall-motion abnormality in the affected cardiac region (Figure 7) [38, 44].

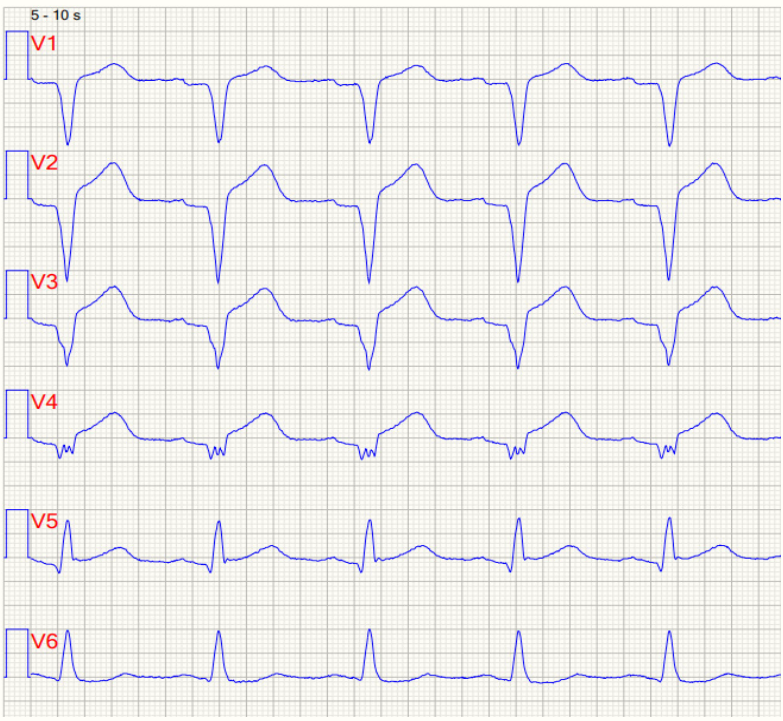


Figure 6. Anterior ST elevation myocardial infarction (STEMI). ECG with anterior ST elevations in leads V2-V4.

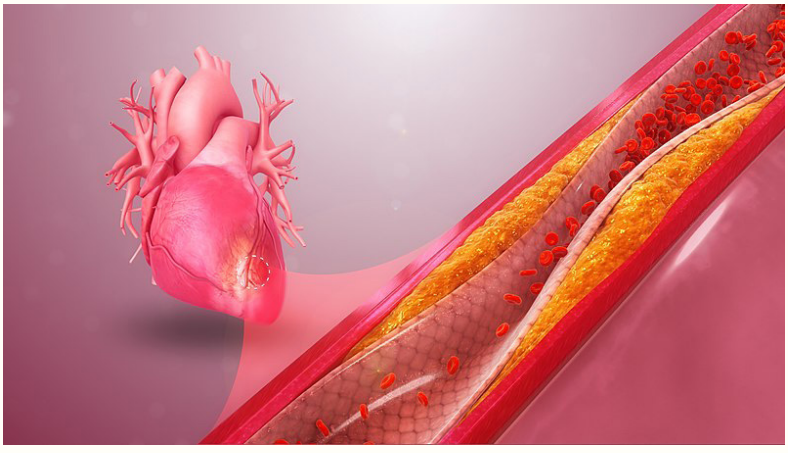


Figure 7. Atherosclerosis. Narrowed epicardial artery lumen due to atherosclerotic plaque. Link to original https://commons.wikimedia.org/wiki/File:Coronary_Artery_Disease.jpg . Used in accordance with CC BY 4.0: https://creativecommons.org/licences/by/4.0/

Coronary microcirculation

Although coronary artery disease is often attributed to obstruction of the large epicardial arteries, the role of the coronary microcirculation (Figure 8) in AMI/STEMI has been highlighted in recent years. Anatomically, the epicardial arteries (>400 μm) branch out to pre-arterioles (100-400 μm) and arterioles (40-100 μm), which branch out into the capillary bed (< 10 μm). The coronary arterioles are the primary resistance vessels of the coronary circulation, distributing and regulating to coronary blood flow to meet the demand of the myocardial tissue. In coronary microvascular dysfunction, functional disturbances in arteriolar tone (caused by mechanisms including endothelial dysfunction and/or smooth muscle cell disturbances) leads to attenuated vasodilatory response to physiological stimuli, which may result in pathological microcirculatory spasm/obstruction. [49]

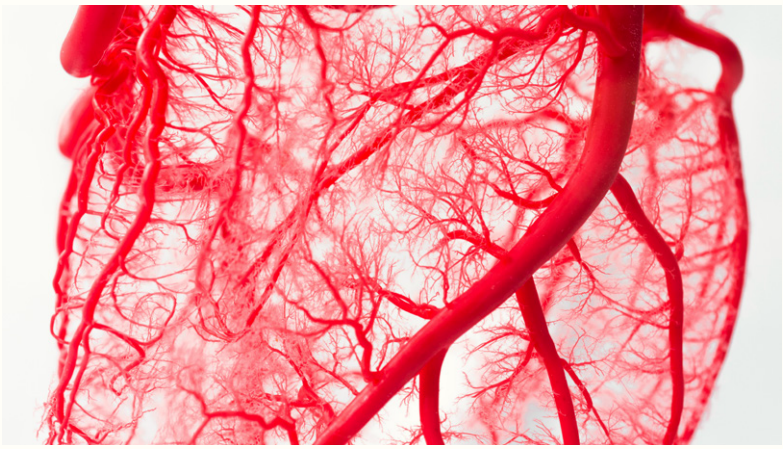


Figure 8. Coronary macro and micro-circulation. Illustration of the larger epicardial coronary arteries branching out to the microvascular circulation.

When blood flow is restored in an obstructed coronary epicardial artery (e.g. through PCI), the blood flow to the ischemic area may still be obstructed. This obstruction of blood flow to myocardial tissue, despite restoration of epicardial blood flow, is termed *no-reflow*. The no-reflow phenomenon is caused by disturbances at the microvascular level, probably mainly through time-dependent structural damage to microvasculature/vascular endothelium caused by prolonged ischemia; or by fibrin/platelet/leukocyte obstruction [50].

In STEMI, impaired microvascular perfusion after restoration of epicardial blood flow will lead to persistent ST elevation, in contrast to the resolution of ST elevation seen after restoration of blood flow at the myocardial tissue level [50]. From an electrophysiologic perspective, this persistent ST elevation indicates persistent transmural ischemia (covered in greater detail under section 1.3.3) [51-53].

1.2.3 TREATMENT

After evaluation of bleeding risk, patients presenting with ACS should receive antiplatelet therapy, in the form of early dual anti-platelet therapy (DAPT). The cornerstone is aspirin in a loading dose as pre-treatment, and thereafter a daily maintenance dose (75-100 mg). The recommended DAPT consists pf aspirin in combination with a $P2Y_{12}$ inhibitor (ticagrelor or prasugrel), or clopidogrel if $P2Y_{12}$ inhibitors are contraindicated. [44, 47]

There is agreement and evidence in guidelines to start aspirin as a pre-treatment immediately when ACS is established. However, there are regional differences, and extensive discussion in guidelines, regarding the timing of DAPT, i.e. when to administer the $P2Y_{12}$ inhibitor or Clopidogrel. According to focused DAPT guidelines, although definitive evidence is lacking, DAPT should "start as soon as possible and deemed safe for clopidogrel and ticagrelor or after the indication for PCI is established based on coronary anatomy for prasugrel". According to recent guidelines for NSTEMI, routine pre-treatment with $P2Y_{12}$ is not recommended in patients non-ST elevation ACS with unknown coronary anatomy who are subjected to early invasive management. [44, 47, 54]

Patients with suspected STEMI should be treated according to guidelines for ACS/STEMI and be referred for immediate coronary angiography under continuous ECG monitoring. DAPT (see above regarding timing) and anticoagulation therapy (routinely as a bolus of unfractionated heparin) should be administered. Oxygen is indicated in hypoxic patients (oxygen saturation <90%) and morphine should be given if necessary for relief of pain. When STEMI diagnosis is established through coronary angiography, reperfusion through primary PCI is

recommended for patients within 12 hours of symptom onset (within 120 minutes of STEMI diagnosis). [44]

The treatment of microvascular dysfunction and no-reflow in STEMI is an area of development, including reducing micro-embolic events with aggressive antiplatelet therapy, targeting microvascular dysfunction/vasospasm (through e.g. intracoronary adenosine) and therapeutic hypothermia. [55, 56]

1.3

TAKOTSUBO SYNDROME VERSUS ACUTE MYOCARDIAL INFARCTION

TS and AMI have similar initial symptoms (such as chest pain and/or dyspnoea), non-invasive test result and complications. Both conditions can present with ST elevation on ECG and are associated with life-threatening ventricular arrhythmia and death [5]. In TS, the myocardial dysfunction is generally extensive and with a distribution beyond the territory of a single epicardial artery. In relation to the extensive cardiac dysfunction, cTn elevation in TS is disproportionally low (with AMI as the reference) [5, 7]. The magnitude of cTn elevation is generally lower, whereas the magnitude of N-terminal-pro hormone BNP (NT-proBNP) elevation is generally larger, in TS compared with AMI [57].

For several reasons, it is important to distinguish TS from AMI (Figure 9). Because of the close resemblance with AMI, TS patients are subjected to antiplatelet and/or anti-coagulative treatment [5]. However, this cardiac-specific treatment may be detrimental because of underlying triggers such as cerebral haemorrhage or other severe bleedings. Also, anti-thrombotic treatment without indication may *cause* bleeding. Another important issue in this context is that serious medical conditions may be masked by symptoms or diagnostic findings of TS (ECG and/or echocardiographic changes, elevation of cTn/NTproBNP). Therefore, an underlying critical illness may be missed at presentation. Lastly, patients with severe AHF are often subjected to treatment with inotropic agents, which may worsen AHF in TS [15].

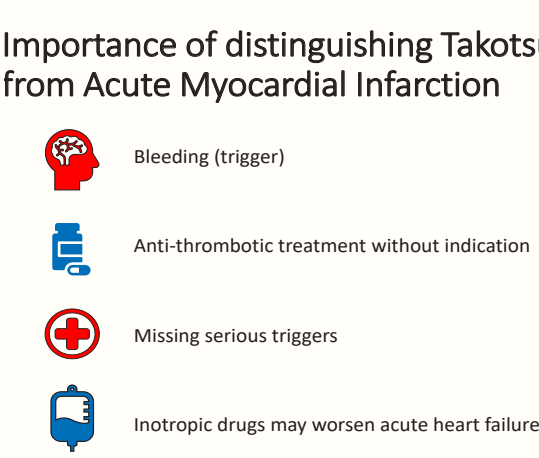


Figure 9. Important reasons for distinguishing Takotsubo syndrome from acute myocardial infarction.

1.3.1 SEX DIFFERENCES

Obstructive coronary artery disease is less common in women compared with men across all age groups. STEMI is more common in younger age-groups compared with older, and less common in women

compared with men. Also, women up to 70 years old have less coronary endothelial dysfunction compared with men [44, 58]. Although incompletely investigated, some studies point toward microvascular and autonomic dysfunction playing a larger role for IHD in women (mainly post-menopausal) compared with men [58, 59]. Regarding both atherosclerotic thrombus formation and endothelial dysfunction, high oestrogen levels in women prior to menopause is thought to have a protective role. This is supported by research showing later onset of atherosclerosis in women compared with men [44, 59]. The protective effects of oestrogen will not be covered extensively in the present thesis, but includes promoting re-endothelization, better balance between vascular injury and repair, decrease of systemic vascular resistance and prevention of coronary vascular spasm.

The female predominance in TS is well-known, where women over the age of 55 years have a 5-fold higher risk of TS compared with women under the age of 55 years. The role of oestrogen in TS remains to be further investigated, but previous studies have indicated a protective effect of oestrogen through attenuating catecholamine-induced vasoconstriction and decreasing sympathetic tone [5].

1.3.2 ELECTROCARDIOGRAPHY

ECG on admission is similar in TS and AMI [14]. Several ECG criteria has been proposed to distinguish TS from STEMI, none of which can separate the two conditions reliably enough to avoid coronary angiography to exclude coronary artery occlusion [5].

ST segment elevation may develop early after symptom onset in TS, and is seen on admission in 44% of cases according to a large cohort [11]. However, there is large variation in previous literature regarding

the presence of ST elevation on admission in TS, ranging from 11 to 100% [60]. Therefore, it is especially challenging to differentiate TS from STEMI based on ECG.

It has been suggested in previous literature that ST elevation in TS follows the regional distribution of wall-motion abnormality [14]. Some studies have shown lower occurrence of ST elevation in atypical than typical TS, however, in larger studies such a difference was not observed [61, 62]. Although it may be reasonable to believe that ST elevations follow the pattern of wall-motion abnormality in TS, no studies have investigated the lead-specific distribution of ST elevation in typical versus atypical TS.

Regarding other ECG changes, T wave inversion has been observed early in both TS and STEMI, although it is more common in the subacute phase in both conditions [14]. Although more common in TS than STEMI, prolongation of the QT interval is seen in both conditions [14, 51]. Conversely, ST depression (and "reciprocal ST depression") is less common in TS compared with STEMI. Pathological Q waves have traditionally been attributed to manifest myocardial infarction in AMI/STEMI [63], however, pathological Q waves have been observed in approximately 15% of patients with TS [14].

Since the exact pathophysiology of TS is incompletely understood, the electrophysiological basis for ECG changes in TS is also unclear. In AMI, the electrophysiological explanations for ECG changes are attributed to myocardial ischemia and/or necrosis [5, 7, 52]. The mechanisms underlying ECG changes observed in AMI are presented below.

1.3.3 ISCHEMIA AND ELECTROCARDIOGRAPHIC CHANGES

ECG changes in ischemia are dependent of the severity and duration of ischemia, the regionality of the ischemic lesion and any other underlying abnormality (such as pre-existing cardiac disease or electrolyte imbalance). In type I AMI, reduced coronary blood flow leads to hypoxia in the affected cardiomyocytes (i.e. ischemia). In short, hypoxia leads to cellular metabolic dysfunction with depletion of ATP (adenosine triphosphate) and accumulation of lactate acid. This causes altered function in the sodium/potassium pump with flow of potassium out of the cell in exchange for sodium, which in turn causes calcium overload. The electrophysiological effects include altered depolarization, slow conduction and early repolarization. Ischemia leads to electrophysiological (and mechanical) changes in the heart whereas myocardial necrosis leads to electrical inactivity [52, 64].

Deviation of the ST segment

After the QRS complex (reflecting ventricular depolarization) the ECG returns to its baseline. Although the ventricles are depolarized in this phase, healthy myocardial cells all reach the same the same potential, and there are no electrical currents recorded by the ECG electrodes. Therefore, under normal conditions, the ST segment will be isoelectric ("flat-line" with no deviation of the ST segment) until repolarization (reflected by the start of the T wave). However, during acute ischemia potassium will leak out of the cell, the resting membrane potential will decrease and the action potential of injured cells will be shortened. This leads to an "injury current", caused by a voltage gradient between normal and ischemic zones. This current is observed on the ECG as ST deviation. [51-53, 63]

There is not full agreement regarding the exact electrophysiological mechanism of ST deviation on the surface ECG. However, the two

main theories (as separate mechanisms or acting simultaneously) are downward shift of the isoelectric line (the "diastolic current theory") or upward shift of the ST segment (the "systolic current theory") in ST elevation, and the inverse relationship in ST depression. Both theories are presented in Figure 10. [51-53, 63]

During the electrical diastole (in the "resting state"), the diastolic current is proposed to arise from a voltage gradient between partially depolarized ischemic myocardial cells and fully repolarized adjacent myocardial cells unaffected by ischemia. This causes an injury current in the resting state and a shift of the isoelectric line, giving the impression of ST deviation. The systolic theory states that (in addition to altered resting membrane potential) ischemic injury shortens the action potential of injured cells. The shortened action potential causes the ischemic cells to repolarize faster than cells unaffected by ischemia, resulting in a voltage gradient between ischemic and healthy cells. This voltage gradient results in an injury current during the ST interval resulting in primary ST segment deviation. [51-53, 63]

In electrical diastole of transmural ischemia, the overall injury vector will be directed away from the recording electrode (causing downward shift of the isoelectric line and ST elevation), whereas in electrical diastole of sub-endocardial ischemia the overall injury vector will be directed towards the electrode (causing upward shift of the isoelectric line and ST depression). The alternative systolic injury currents are directed in the inverse direction, causing upward and down shift of the ST segment. [51-53, 63].

Of note, ST elevation is not limited to STEMI or TS. It also occurs in e.g. coronary artery dissection, peri(myo)carditis and coronary artery/microvascular spasm [44, 65]. In pericarditis, PR segment depression/ST segment elevation is attributed to subepicardial injury or atrial in-

jury resulting in a current away from the electrode in diastole, and a downward shift of the isoelectric line, which is seen as ST elevation on the surface ECG. Thus, although transmural ischemia is the primary source of ST elevation, isolated epicardial injury/ischemia also has the prerequisite of causing ST elevation [65-67].

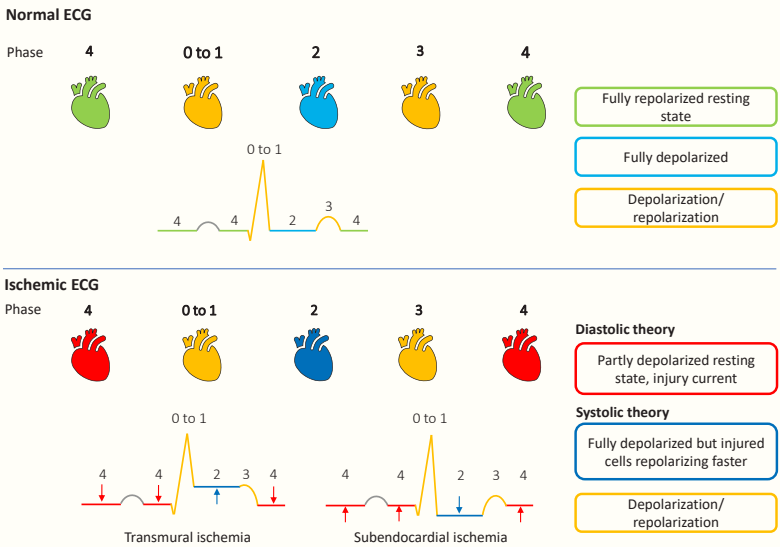


Figure 10. ST deviation. Electrophysiology of ST elevation and ST depression. ECG = electrocardiography.

Reciprocal ST depression

During transmural ischemia (with ST elevation according to the principles described above), ST segment depression can occur in leads reflecting the contralateral region of the heart. These ST depressions are generally termed "reciprocal ST depressions" (figure 11) [52]. Previous research has attributed reciprocal ST depression to contralateral ischemia (due to collateral vessels diverting blood to the primary ischemic area), multivessel disease or as an electrophysiological "mirror" phenomenon. However, research specifically addressing re-

ciprocal ST depression/ST changes has indicated that reciprocal ST changes are likely an electrical phenomenon and not caused by distant ischemia [68-70].

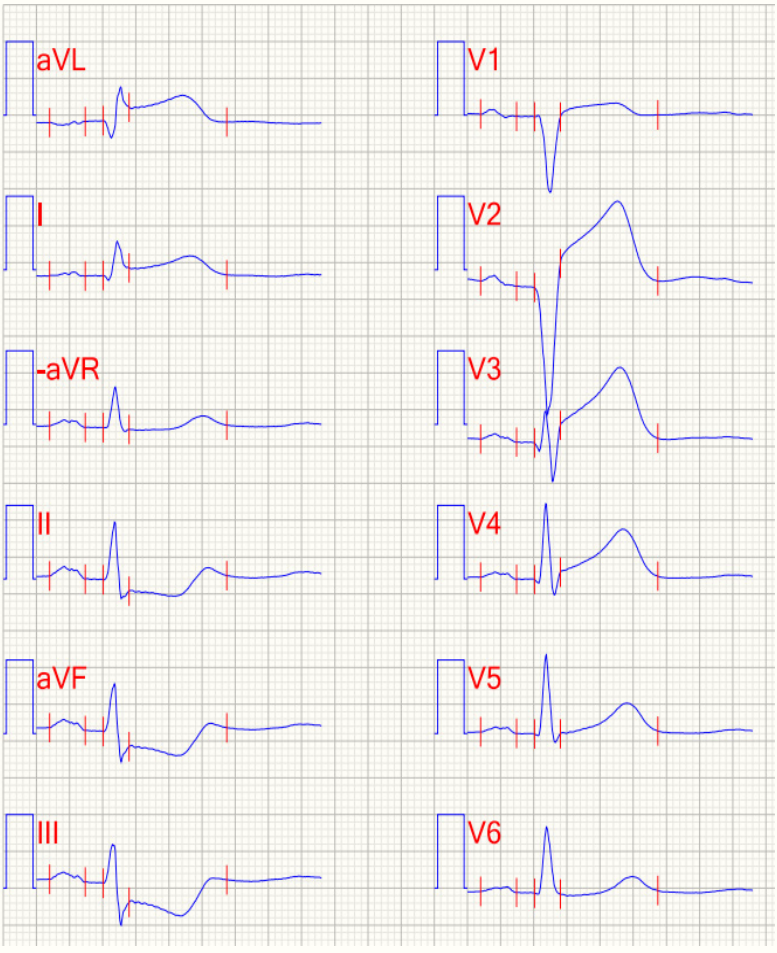


Figure 11. Reciprocal ST depression. Electrocardiography (ECG) with antero-lateral ST elevations in leads V2-V4 and aVL-I with reciprocal inferior ST depressions in leads II-aVF-III.

T wave inversion

The T wave represents the repolarization of the ventricles. In each individual cardiomyocyte, the repolarization current moves in the opposite

direction of the depolarization current, and would therefore generate a deflection in the opposite direction of the QRS complex (if a voltmeter measures the current over a single myocardial cell). However, in a normal ECG the T wave is concordant with the QRS complex, i.e. both the net QRS amplitude and T wave are positive in the majority of ECG leads. Since the ECG equipment measures the depolarization wave over the entire heart, it is the sum of electrical forces from each cell that is recorded. The duration of the action potentials of the cells near the inner endocardium are more prolonged than the cells near the outer epicardium. Thus, whereas the epicardial cells are the last to depolarize they are the first to repolarize, resulting in a repolarization wave in the opposite direction of the depolarization wave. This transmural repolarization gradient explains the concordance of T wave and QRS complex. [52, 63, 71]

Peaked and wide T waves ("hyperacute" T waves) accompanied by QT prolongation (sometimes with a small ST depression), is an early ECG change in transmural ischemia, occasionally preceding ST elevation. This T wave pattern is explained by prolonged action potential duration and delayed repolarization in the endocardium, which is in turn a consequence of the initial subendocardial ischemia caused by total coronary occlusion. Although incompletely understood, flat or negative T waves observed in the sub-acute phase of ischemia reflect alterations of depolarization as well as delayed repolarization of the epicardium, as a consequence of the progression from subendocardial to subepicardial ischemia. [51, 52].

QT prolongation

Prolongation of the QT interval often accompanies T wave inversion in the sub-acute phase of ischemia/AMI. Since the QT interval extends from onset of the QRS complex to the end of the T wave, it represents the whole sequence activation and recovery of the ventricles. Because

ischemia in the sub-acute phase of AMI is associated with increased action potential duration, the QT interval is prolonged. [52]

Pathological Q waves

In leads overlooking infarcted tissue pathologic Q waves appear, because necrotic muscle does not generate electrical forces. Therefore, the ECG electrode over the infarcted region detects electrical currents from the opposite side of the heart (directed away from the electrode), generating a deep initial negative deflection of the QRS complex [63].

1.3.4 LIFE-THREATENING VENTRICULAR ARRHYTHMIA

Life-threatening ventricular arrhythmia (LTVA) or life-threatening arrhythmia (LTA) are generally defined as sustained ventricular tachycardia or ventricular fibrillation (VF), although "cardiac arrest", asystole or high-degree atrioventricular block are sometimes included [14, 72-77]. In both TS and STEMI, left ventricular dysfunction is associated with an increased occurrence of LTVA [78-81].

The reported occurrence of LTVA in TS varies substantially, between 2.0% and 13.5 % [14, 72, 73, 82]. Importantly, in patients diagnosed with TS after presenting with LTVA and/or cardiac arrest, it is difficult to establish if TS caused the arrhythmia, or if TS was a consequence of the treatment/resuscitation with possible administration of catecholaminergic drugs [14, 74]. In STEMI, LTVA has been reported to occur in 3-6% of cases following intervention [44, 83]. Ventricular arrhythmias are more common in male patients with STEMI compared with females [84]. This is relevant when comparing LTVA between TS and STEMI, because over 90% of patients with TS are female [5].

The pathophysiological basis for LTVA in TS is largely unknown.

Catecholamine toxicity and/or ischemia has been proposed as cause of LTVA in the acute phase, whereas myocardial oedema and/or acquired long QT syndrome has been proposed as a cause of LTVA in the subacute phase [74, 85, 86]. Myocardial oedema as a substrate for LTVA in TS is based on the observation of transient transmural left-ventricular oedema on cardiac magnetic resonance imaging (CMR) [87], which has been correlated with T wave inversion and QT prolongation. This has in turn been theorized as reflecting delayed/dispersed repolarization leading to local re-excitation, hypothetically playing a role in LTVA in TS [14, 74, 87].

The pathophysiological basis for LTVA in STEMI is ischemia. Both ischemia and reperfusion disturb the ionic balance of the myocardial cells through ATP depletion, anaerobic metabolism with lactate acid accumulation and elevation of extracellular potassium. The downstream electrophysiological effects can lead to LTVA through mechanisms including early (post-depolarization) ectopic beats, dispersion of repolarization, re-entry and short action potential durations [83].

Although several studies have demonstrated an association between QT prolongation and LTVA in TS [14], previous research on this subject is somewhat conflicting. While some studies have demonstrated an association between QT prolongation and LTVA [14, 88], others have shown no association [78] or the inverse association (i.e. less arrhythmia with QT prolongation) [89]. With the exception of QT prolongation, the literature is scarce on ECG predictors of LTVA specifically in TS. However, increased QRS duration [78] and prolonged Tpeak to Tend [90] have been associated with LTVA in TS. In STEMI, many ECG changes have been proposed as predictors of LTVA, such as Tpeak to Tend [91, 92], the extent of resolution of ST elevation [93]; increased QRS duration and dispersion of QRS [94, 95]; and complete atrioventricular block [96].

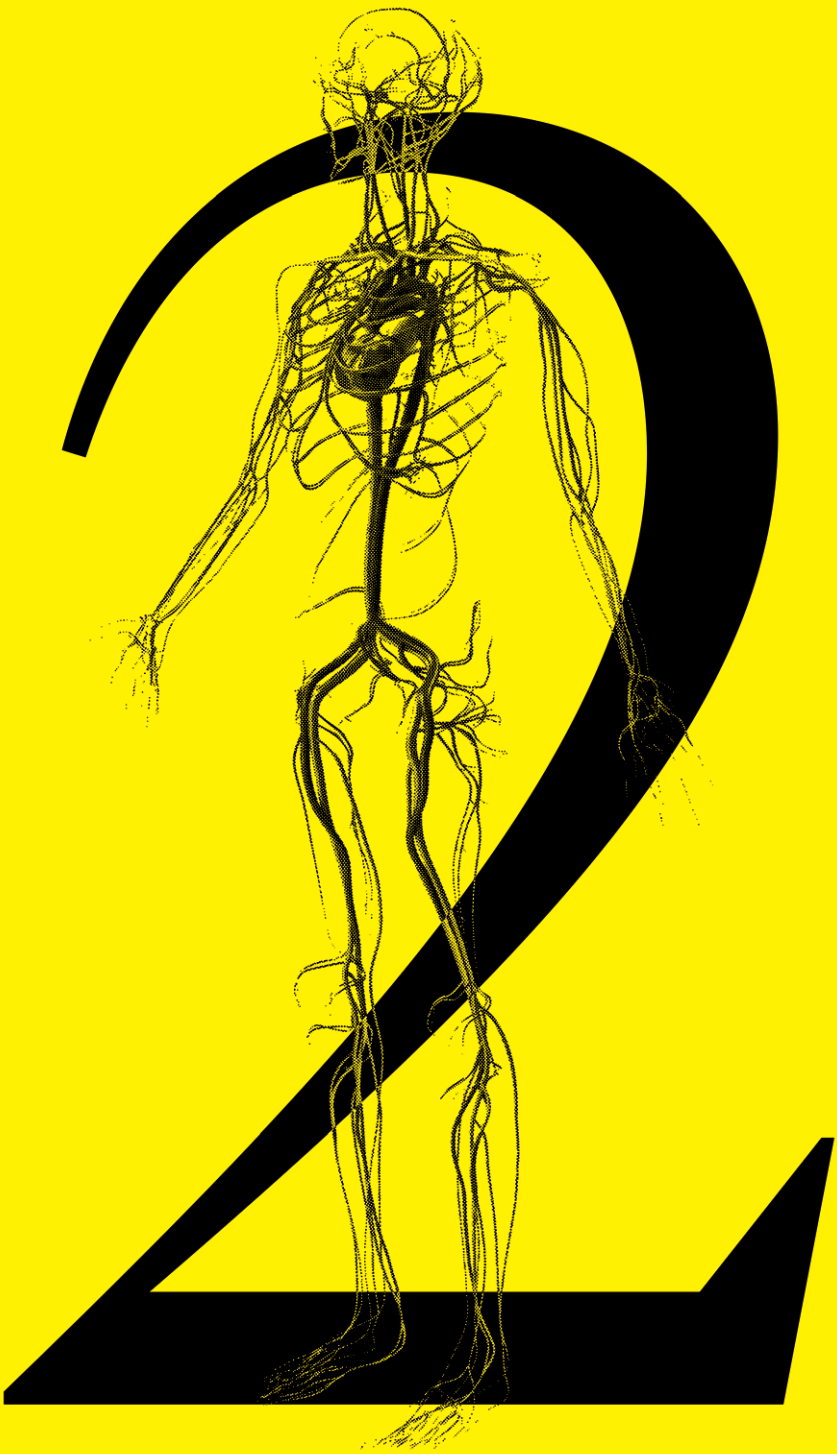
1.3.5 MORTALITY

The mortality in STEMI has decreased parallel with increasing use reperfusion therapy (mainly PCI), modern anti-thrombotic therapy and improved secondary prevention [44]. Currently, in-hospital mortality varies from 4 to 12% in the European Society of Cardiology (ESC) countries and from 5 to 6% in the United States (US). The corresponding numbers for 1-year mortality is approximately 10% and from 7 to 18% respectively [44, 45].

Studies investigating the mortality in TS [11, 97] has been compared to other sources presenting mortality figures for AMI, suggesting similar mortality [14, 44, 45, 98]. A large study has shown a yearly death rate of 5.6% in TS [11]. Recent research has shown that 30-day all-cause mortality was lower in NSTEMI, but higher in STEMI, compared with TS [99]. However, there are large discrepancies between studies comparing mortality between AMI and TS, with STEMI, NSTEMI or TS showing the highest mortality depending on study [99-103].

It is important to note that TS is associated with other severe medical conditions [14], which complicates the interpretation of mortality figures. The highest in-hospital mortality in TS is seen in patients presenting with cardiogenic chock or cardiac arrest, where in the latter it is difficult to say whether TS was the cause or the consequence [6]. A meta-analysis found an all-cause in-hospital mortality rate of 4.5% in TS, whereof 38% was directly related to TS (mainly through ventricular arrhythmias and acute heart failure/cardiogenic shock) and the remaining 62% was related to non-cardiac conditions. In the same study, male sex was associated with higher mortality; and most importantly, secondary TS (due to other underlying conditions) was associated with a 10-fold increased risk of mortality compared with primary TS. [104]. Another large study concluded that 81% of patients with in-hospital

mortality had underlying critical illness, where males had higher mortality compared with females, likely explained by higher prevalence of underlying critical illness in males [105].



AIM

"The greater danger for most of us lies not in setting our aim too high and falling short; but in setting our aim too low, and achieving our mark."

Michelangelo

The overall aim of this thesis was to investigate electrocardiographic characteristics and in-hospital outcome in Takotsubo syndrome versus ST elevation myocardial infarction, and to put these observations into perspective of the pathophysiology of Takotsubo syndrome. The aims of the respective studies included in this thesis are listed below.

I. To investigate the association between T wave inversion and Major Adverse Cardiac Events in patients with Takotsubo syndrome.

II. To compare the occurrence of life-threatening ventricular arrhythmia or death within 72 hours from admission in patients with Takotsubo syndrome versus age and sex matched patients with ST elevation myocardial infarction.

III. To compare admission electrocardiographic changes, and electrocardiographic predictors of life-threatening ventricular arrhythmia or death, within 72 hours from admission in patients with ST elevation Takotsubo syndrome versus age and sex matched patients with ST elevation myocardial infarction.

IV. To prospectively confirm the results of aim III, and to investigate the temporal pattern of T wave inversion, ST elevation, Q wave pathology and QT prolongation in female patients with Takotsubo syndrome versus anterior ST elevation myocardial infarction.

PATIENTS, METHODS AND RESULTS

"He who would learn to fly one day must first learn to stand and walk and run and climb and dance; one cannot fly into flying."

Friedrich Nietzsche

3.1

INTRODUCTION TO PATIENTS AND METHODS

The first step of the present thesis was the establishment of a database of all TS patients treated at Sahlgrenska University Hospital (Gothenburg, Sweden) since TS ("suspected stress cardiomyopathy") was introduced in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) in 2008. Therefore, 2008 was chosen as the starting point, and patients treated until 2019 where included, corresponding to when data collection was finalized for study I. Patients were identified through SCAAR, but the information registered in our database was the result of comprehensive analysis of all patients' medical charts; echocardiographic, angiographic and telemetry reports; as well as detailed analysis of all in-hospital ECGs.

After establishing the TS database, these patients were subsequently age and sex matched 1:3 against patients with STEMI treated at Sahlgrenska University Hospital during the corresponding time period. For the purpose of study II, comprehensive analysis was performed of all STEMI patients' medical charts, as well as echocardiographic, angiographic and telemetry reports. In addition to this, in-hospital ECGs were analysed in detail for all STEMI patients, for the purpose of study III. Study IV was a sub-study to the larger multicentre prospective

STAMI (Stunning in Takotsubo and Acute Myocardial Infarction) study. For the ECG part of the STAMI project, we prospectively included patients for temporal ECG analysis with head-to-head comparison between TS and anterior STEMI.

In all studies, data was registered in a pre-defined electronical case report form (eCRF). The eCRF was accompanied by a dictionary with detailed definitions of all variables from start of data collection. In study IV, the eCRF was developed and incorporated as an online platform (REDCap version 10.6.1 ® Vanderbilt University) within the Gothenburg University servers.

All studies were approved by the Swedish Ethical Review Authority. Study I-III is covered by registry number 2019-02459 (with addendum 2020-01569) and study IV is covered by registry number 2020-06257 (with addendum 2021-01921). Patients in all studies were pseudonymized and assigned a research identification code, and the identification key was stored in a safe data environment.

3.2

STUDY I

Study cohort and data collection

In study I, ECG and ECG predictors of outcome was investigated in patients with TS. All patients admitted to Sahlgrenska University

Hospital with suspected TS from June 2008 to February 2019 (N=236) were identified using SCAAR as described above. The suspicion of TS in SCAAR is based on the Gothenburg criteria of TS [106], which is similar to the later established ESC criteria [7].

Patient medical charts; as well as echocardiographic, angiographic and telemetry reports; were reviewed for all patients in order to confirm the diagnosis according to ESC criteria [7]. All patients underwent coronary angiography to exclude coronary occlusion as the cause of myocardial dysfunction. For patients with confirmed TS, information was collected regarding age, sex, triggers; symptoms, severity of heart failure and clinical parameters on admission; pre-admission medication; echocardiographic parameters; arrhythmia from admission to discharge and mortality. All medical charts were reviewed by two independent physicians.

All 12-lead ECGs from admission to discharge, as well as a baseline ECG before the TS event, were analysed by two independent physicians for all patients. Data regarding comorbidities and smoking status was extracted from SCAAR and merged with the data in the eCRF.

Method of ECG analysis

Aside from T wave inversion and the lead-specific ST-T changes, the following ECG parameters were collected: date and time of ECGs; rhythm, heart rate; QRS and T wave axis; PQ interval, QRS duration, QT interval, P wave morphology, atrioventricular conduction, Q wave pathology; QRS morphology and amplitude and ST deviation.

12-lead ECGs were recorded at a paper speed of 50 mm/s and an amplification of 10 mm/mV. Lead specific T wave amplitude and ST-T changes (ST deviation) were measured manually from the isoelectric line to peak or nadir to the nearest 0.5 millimetre. The peak of ST ele-

vation was measured at the J-point and the nadir of ST depression was measured at 60 milliseconds after the J-point.

Electronically derived values for heartrate, PR interval, QRS duration, QRS axis, T wave axis and QT time were chosen if assessed manually as correct. The corrected QT interval (QTc) was calculated using Bazzet's formula.

Endpoints and definitions

The primary endpoint was in-hospital Major Adverse Cardiac Events (MACE). In the present study, MACE was defined as the composite of in-hospital death, any ventricular tachycardia (VT, sustained or non-sustained), ventricular fibrillation (VF) or clinically significant bradycardia (defined as atrioventricular ≥2 or asystole >10 seconds). All ECG definitions are summarized in Table 2.

Table 2. Electrocardiographic definitions.

Variable	Definition
Rhythm	Sinus rhythm or atrial fibrillation/flutter
Heart rate	Beats per minute.
PR interval	The time from the onset of the P wave to the start of the QRS complex (milliseconds).
P wave morphology	Normal P waves should be upright in leads I and II, ≤2.5 millimetres tall and ≤120 milliseconds wide. P pulmonale = P waves >2.5 millimetres tall and ≤120 milliseconds wide. P mitrale = P waves ≤2.5 millimetres tall and >120 milliseconds wide.
QRS duration	The duration from start to end of the QRS-complex (milliseconds).
QRS or T wave axis	Axis in degrees.

QRS morphology	Normal QRS ≤120 milliseconds wide. Right bundle branch block = QRS >120 milliseconds wide, RSR' pattern in V1-3, wide, slurred S wave leads I, aVL, V5-6. Left bundle branch block = QRS >120 milliseconds wide, dominant S wave in V1, broad monophasic R wave in leads I, aVL, V5-V6, absence of Q waves in leads I, V5-V6, prolonged R wave peak time >60ms in leads V5-6,
QT time	The time from the start of the Q wave to the end of the T wave (milliseconds).
ST elevation	≥1 millimetre elevation of the ST segment measured from the J-point to the isoelectric line in any two consecutive leads.
ST depression	≥1 millimetre depression of the ST segment measured 60 milliseconds after the J-point to the isoelectric line in any two consecutive leads.
ST elevation with reciprocal ST-depression	Opposite leads: Inferior (II, aVF, III) versus lateral (aVL, I and/or V5, V6) or antero-lateral (V1-V4 + aVL, I and/or V5, V6).
T wave inversion	Negative T-wave with depth >1 millimetre in any lead except V1.
Q wave pathology	Negative deflection preceding R-wave with duration >40 milliseconds or >2 millimetres deep or >25 % of QRS amplitude in two anatomically consecutive leads.
Long QTc	QTc duration >440 milliseconds in males and >460 milliseconds in females.
Low voltage QRS	QRS complex with amplitude ≤5 millimetres in all limb leads or ≤10 millimetres in all precordial leads.

Statistical analysis

Patients were categorized as those with or without in-hospital MACE. Differences in continuous variables were tested with Mann-Whitney U test for non-normally distributed variables and Student's t-test for normally distributed variables (as assessed by inspection of histograms and tested with Shapiro-Wilk test). Categorical variables were com-

pared using Fisher's exact test. The age- and sex-adjusted association between T wave inversion on admission and MACE was tested with logistic regression including age and sex as covariates. In addition, this association was further assessed in four propensity score (PS) adjusted models *(Figure 12)*, including different covariates when calculating PS.

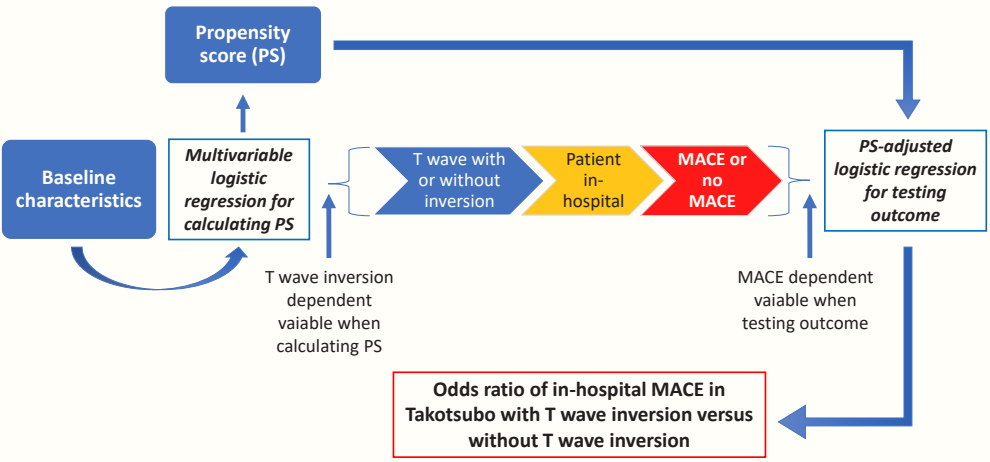


Figure 12. Propensity score model. Conceptual scheme of the propensity score model.

The propensity scores included the following variables:

- *Primary PS-adjusted model:* sex, diabetes, age, hypertension, hyperlipidaemia, smoking status (current, former or never) and sinus rhythm versus non-sinus rhythm on the admission ECG.

- *PS-adjusted sensitivity model I:* Sex, diabetes, age, sinus rhythm versus non-sinus rhythm on the admission ECG, somatic trigger versus emotional trigger or no trigger, cardiogenic shock (defined as Killip class IV) at presentation, acute heart failure (defined as Killip class ≥II) at presentation, left ventricular ejection fraction at presentation.

- *PS-adjusted sensitivity model II:* Sex, age, somatic trigger versus emotional trigger or no trigger, sinus rhythm versus non-sinus rhythm on admission ECG, left ventricular ejection fraction at presentation, cardiogenic shock, Typical versus atypical takotsubo morphology.

- *PS-adjusted sensitivity III:* Sex, age, sinus rhythm versus non-sinus rhythm on admission ECG, acute heart failure at presentation, left ventricular ejection fraction at presentation.

- *PS-adjusted sensitivity IV:* Sex, age, somatic trigger versus emotional trigger or no trigger, typical versus atypical takotsubo morphology.

The statistical analyses were performed in SAS (version 9.4) or Python (version 3.7). The level of significance was set at p-value < 0.05.

Results

A total of 215 patients who fulfilled ESC diagnostic criteria for TS were included in study I (mean age 69 ± 13 years, 93% female). Among all TS patients, 181 (84%) patients met the endpoint of in hospital MACE and 34 (16%) patients did not.

Baseline characteristics on admission were similar in patients with and without MACE. The proportion of missing data was low in most variables: Pre-admission medication 3.3%, symptoms and signs 2.8-3.7%, comorbidities 1.4%, ECG variables 0-0.9%, echocardiographic variables 4.7%. There were no missing values in the variables T wave inversion and MACE.

In univariable analysis, non-sinus rhythm/atrial fibrillation, abnormal P wave morphology and absence of T wave inversion was associated with increased occurrence of in-hospital MACE. T wave inversion remained associated with lower risk of MACE after adjustment for age and sex as well as in all PS-adjusted models (Table 3).

Table 3. The propensity score (PS) adjusted association between T wave inversion and adverse cardiac events[1]

Sensitivity models	Odds ratio (95% confidence interval)	p-Value
In-hospital major adverse cardiac events		
Primary PS-adjusted model	0.28 (0.10–0.76)	0.012
PS-adjusted sensitivity model I	0.43 (0.19–0.99)	0.046
PS-adjusted sensitivity model II	0.43 (0.19–0.97)	0.041
PS-adjusted sensitivity model III	0.42 (0.19–0.93)	0.032
PS-adjusted sensitivity model IV	0.42 (0.19–0.95)	0.037
Any in-hospital ventricular tachycardia or fibrillation		
Primary PS-adjusted model	0.24 (0.06–0.094)	0.041
PS-adjusted sensitivity model I	0.33 (0.11–0.98)	0.046
PS-adjusted sensitivity model II	0.34 (0.11–0.98)	0.047
PS-adjusted sensitivity model III	0.33 (0.11–0.93)	0.037
PS-adjusted sensitivity model IV	0.32 (0.11–0.95)	0.040

[1] 107. Jha S, Zeijlon R, Enabtawi I, Espinosa AS, Chamat J, Omerovic E, et al. Electrocardiographic predictors of adverse in-hospital outcomes in the Takotsubo syndrome. Int J Cardiol. 2020;299:43-8.

3.3

STUDY II

Revised total number of TS patients

In study II, patients with TS (total TS, N=215) from study I were matched against patients with STEMI. The youngest TS patient could not be age and sex matched with any STEMI patient from the corresponding time period, and this TS patient was therefore excluded (total TS, N=214). In the submission-review process of study II, an extensive re-review of all patients with TS was performed. In this re-review, we identified one TS patient who was discharged early in whom the TS diagnosis was considered very likely, but not explicitly validated. Therefore, this patient was also excluded (total TS, N=213).

Study cohort and data collection

In study II, the occurrence LTVA or death within 72 hours from admission was compared between TS and STEMI. As covered above, a control group of STEMI patients corresponding to the TS cohort were identified using SCAAR. Each patient with TS from study I (N=213, after exclusion of two TS patients as explained above) were age and sex matched against three patients with STEMI (N=639). After review of patient medical charts for all matched STEMI patients, 43 patients were excluded because the STEMI diagnosis could not be validated according to ESC guidelines, leaving a total of 596 patients in the matched STEMI cohort.

From the matched TS – STEMI cohort, one patient with confirmed anterior STEMI and one patient with confirmed non-anterior STEMI,

was selected per matching patient with TS. If a TS patient could not be matched with both an anterior and a non-anterior STEMI patient, these patients were not included, resulting in a 1:1:1 matched cohort (Figure 13).

Clinical, echocardiographic and angiographic data, as well as parts of the ECG data, described in study I were collected through comprehensive review of included STEMI patients' medical charts. In addition to the analysis of telemetry reports from study I, data regarding sustained and non-sustained VT were collected for both the TS and STEMI cohort, to obtain a more precise measure of VT (in contrast to any VT in study I). We also collected data regarding prior arrhythmic burden, as well as resuscitation on admission/in-hospital and/or the occurrence of defibrillation or cardioversion, for both the TS and STEMI cohort. Information regarding comorbidities was obtained from SCAAR.

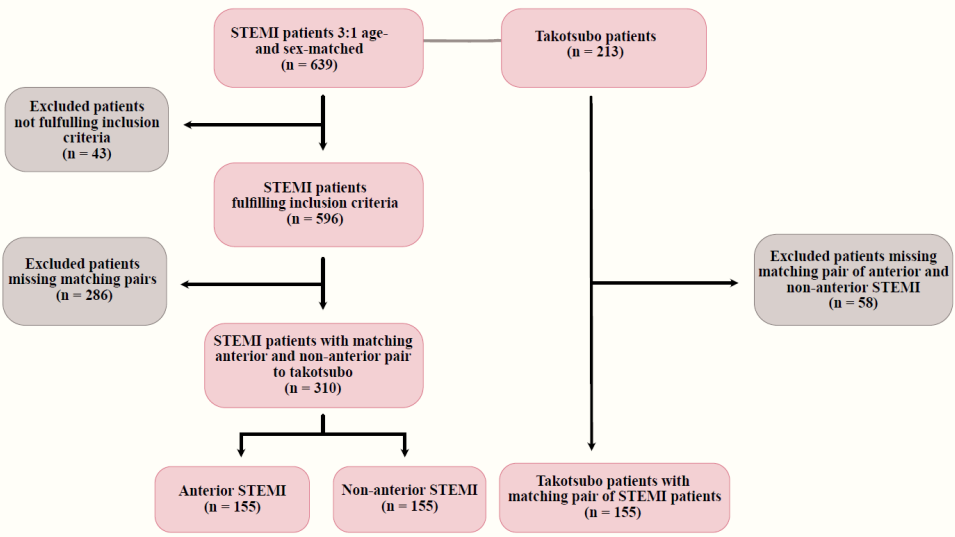


Figure 13. Inclusion flow chart of study II.[2]

[2] 108. Zeijlon R, Chamat J, Enabtawi I, Jha S, Mohammed MM, Wågerman J, et al. Risk of in-hospital life-threatening ventricular arrhythmia or death after ST-elevation myocardial infarction vs. the Takotsubo syndrome. ESC Heart Fail. 2021.

Endpoints and definitions

STEMI was defined as anterior according to the interventional cardiologist's report, where "acute transmural anterior infarction" is assigned as the diagnose code if the patient has culprit occlusion in the left anterior descending artery (LAD). All other STEMI were defined as non-anterior (culprit occlusion in the right coronary artery [RCA] of the left circumflex artery [LCx]). The primary endpoint was the composite LTVA or death within 72 hours from admission. LTVA was defined as sustained VT or VF. Sustained VT was defined as VT with duration >30 seconds or requiring cardioversion/defibrillation. Cardiogenic shock (CS) was defined as Killip Class 4 and acute heart failure (AHF) was defined as Killip Class ≥ 2. QT prolongation was defined as QTc > 440 milliseconds for men and QTc > 460 milliseconds for women. QTc was calculated using Bazett's formula [109].

Statistical analysis

Patients were categorized according to disease type, i.e. TS, anterior STEMI or non-anterior STEMI. Differences in continuous variables were tested with Mann-Whitney U test for non-normally distributed variables and Student's t-test for normally distributed variables. Categorical variables were compared using Chi-Square test or Fisher's exact test.

In univariable analysis, the occurrence of LTVA or death (within 72 hours and between 24 and 72 hours) was compared between TS, anterior and non-anterior STEMI. The adjusted associations between disease type and outcome for TS versus anterior STEMI, and TS versus non-anterior STEMI, were tested using multivariable logistic regression. The covariates included in the multivariable model were diabetes, current smoking, hypertension, previous PCI and previous MI. A random effect was included to account for the correlation within matching triplets.

The statistical analyses were performed in SAS (version 9.4) and SPSS (IBM, version 27). The level of significance was set at p-value < 0.05.

Results

The final age- and sex matched cohort consisted of 155 patients with TS, 155 patients with anterior STEMI and 155 patients with non-anterior STEMI. In all three groups, 91% (141/155) of patients were female. The groups were well balanced with small differences in baseline characteristics between groups.

In univariable analysis, patients with TS had lower occurrence of LTVA or death within 72 hours from admission compared with both anterior (2.6% vs 14%, p=0.0015) and non-anterior (2.6% vs 9.0%, p=0.023) STEMI. The differences in this composite endpoint were primarily driven by a lower occurrence of LTVA within 72 hours in TS compared with STEMI, since we found no significant differences in death within 72 hours between TS and STEMI (1.9% in TS vs 3.9% in both anterior and non-anterior STEMI, p=0.32).

After multivariable adjustment, TS remained associated with a lower risk of LTVA or death within 72 hours compared with STEMI (Table 4).

Table 4. Adjusted risk of adverse outcomes for patients with Takotsubo syndrome (TS) versus anterior or non- anterior ST elevation myocardial infarction (STEMI).[3]

Outcome	Adjusted odds ratio (95% confidence interval)	
	TS vs. anterior STEMI	**TS vs. non- anterior STEMI**
Within 72 h		
LTVA or death	0.19 (0.06 to 0.58)	0.29 (0.09 to 0.93)
VT, VF, or death	0.21 (0.12 to 0.38)	0.16 (0.09 to 0.28)
VT or VF	0.20 (0.12 to 0.36)	0.14 (0.08 to 0.26)
24–72 h		
LTVA or death	0.50 (0.11 to 2.18)	0.51 (0.11 to 2.28)
VT, VF, or death	0.27 (0.14 to 0.52)	0.21 (0.11 to 0.40)
VT or VF	0.24 (0.11 to 0.49)	0.18 (0.09 to 0.36)

3.4

STUDY III

Study cohort and data collection

To address the clinical challenge of distinguishing ECG in patients with ST elevation due to either TS (STE-TS) or STEMI, we included only pa-

[3] 108. Ibid.

tients presenting with ST elevation in study III. For the purpose of this study, the matched population of patients with TS (N=213) and STEMI (N=596) from study II was used. In order to obtain desired representable admission ECGs in study III, exclusion criteria for both TS and STEMI patients were pacemaker rhythm or left bundle branch block (LBBB) on admission; previous coronary artery bypass graft (CABG) or not having ST elevation on admission ECG. If a TS patient fulfilled exclusion criteria, its respective matched STEMI patient/s were also excluded. Patients with STEMI were further subdivided into STEMI with LAD occlusion and STEMI with non-LAD occlusion (Figure 14, patient inclusion flow-chart).

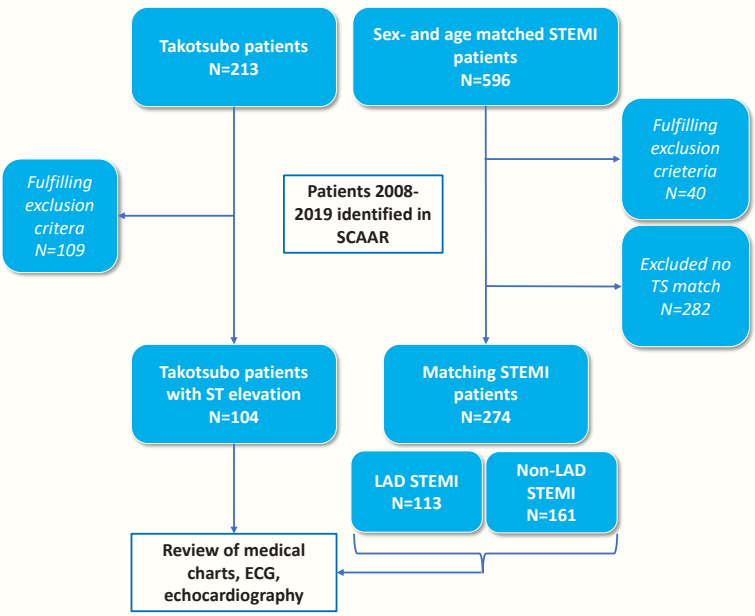


Figure 14. Patient inclusion flow-chart of study III.

Clinical, echocardiographic and angiographic data, as well as data from telemetry reports, were collected for all patients as described under study II. In addition, culprit lesion was registered from the interven-

tional cardiologist's report for all patients with STEMI. Information regarding comorbidities was obtained from SCAAR. For all patients, we analysed 12-lead ECG on admission (before angiography/PCI) and daily ECGs up to 5 days post admission, as well as a baseline ECG before STEMI event when available. Because of large discrepancies regarding the timing and availability of baseline and post-admission ECGs; and due to bias introduced by the indication for recording of these ECGs; only admission ECGs were included in the final analysis. ECGs for the STEMI group were analysed according to the same method described for the TS cohort under study I.

Endpoints and definitions

LAD STEMI was defined as STEMI with culprit lesion in LAD or any of its branches (segments 5-10); and non-LAD STEMI was defined as STEMI with culprit lesion in the right coronary artery (RCA, segments 1-4) or left circumflex artery (LCx, segments 11-14) or any of their branches (segments 15-18 were assessed according to patient-specific anatomy). All basic ECG definitions are summarized above in Table 2 and all additional ECG definitions are summarized in Table 5.

The primary endpoint regarding the analysis of ECG predictors was LTVA or death within 72 hours from admission. As in study II, LTVA was defined as sustained VT or VF (sustained VT defined as VT with duration >30 seconds or requiring cardioversion/defibrillation). Cardiogenic shock (CS) was defined as Killip Class 4 and acute heart failure (AHF) was defined as Killip Class ≥ 2. QT prolongation was defined as QTc > 440 milliseconds for men and QTc > 460 milliseconds for women. QTc was calculated using Bazett's formula.

Statistical analysis

Patients were categorized according to disease type, i.e. TS, LAD STEMI or non-LAD STEMI. Differences in continuous variables were

tested with Kruskal-Wallis test for non-normally distributed variables and ANOVA for normally distributed variables. Categorical variables were compared using Chi-Square test or Fisher's exact test.

For ECG predictors, univariable and multivariable logistic regression was used to test the association between ECG changes and outcome. Multivariable model A included age and sex as covariates and multivariable model B included age, sex, diabetes and previous myocardial infarction as covariates.

All statistical analyses were performed using SPSS version 27 and all plots were created using R-studio version 1.4.1103 *(ggplot, Tidyverse package in R)*. The level of significance was set at $p < 0.05$.

Table 5. ECG definitions in study III.

ST elevation patterns	
Anterior	ST-elevation ≥ 1 millimetre in V1-V2, V2-V3 or V3-V4
Lateral	ST-elevation ≥ 1 millimetre in V5-V6 or I-aVL
Inferior	ST-elevation ≥ 1 millimetre in II-aVF or aVF-III
Anterolateral	ST-elevation ≥ 1 millimetre in V1-V2, V2-V3 or V3-V4 and V5-V6 or I-aVL
Inferolateral	ST-elevation ≥ 1 millimetre in II-aVF or aVF-III and V5-V6 or I-aVL
Anterior-inferior	ST-elevation in V1-V2, V2-V3 or V3-V4 and II-aVF or aVF-III
Anterior-inferior-lateral	ST-elevation in V1-V2, V2-V3 or V3-V4 and II-aVF or aVF-III and V5-V6 or I-aVL
Other	ST-elevation pattern not fitting any of the above mentioned

Predictors of LTVA or death within 72 hours	
Sum of all ST elevations	The sum of the magnitude of ST elevations in all 12 leads in millimetres.
Sum of all ST deviations	The sum of the absolute values of the magnitude of ST deviations (in all 12 leads in millimetres.
Maximum single lead ST elevation	The magnitude of ST elevation in millimetres in the lead (out of all 12 leads) with the maximum magnitude of ST elevation.
ST elevation with reciprocal ST-depression	Opposite leads: Inferior (II, aVF, III) versus lateral (aVL, I and/or V5, V6) or antero-lateral (V1-V4 + aVL, I and/or V5, V6).

Results

The cohort consisted of 104 patients with elevation STE-TS, 113 patients with LAD STEMI and 161 patients with non-LAD STEMI (89% female patients in all groups). The average age was 69 ± 13 years in STE-TS, 71 ± 14 years in LAD STEMI and 68 ± 13 years in non-LAD STEMI. The largest differences in baseline characteristics were a smaller proportion of diabetes (1.0% vs 14%) and lower BMI, in (BMI 24 vs 27), in STE-TS compared with STEMI. More patients presented with dyspnoea (34% vs 11%), and fewer patients presented with angina (68% vs 93%), in STE-TS compared with STEMI.

Comparison of admission ECG

Detailed basic ECG changes, ST elevation pattern on admission (Figure 15); as well as lead-specific ST elevation distribution; (Figure 16) in TS was considerably more similar to LAD STEMI than non-LAD STEMI.

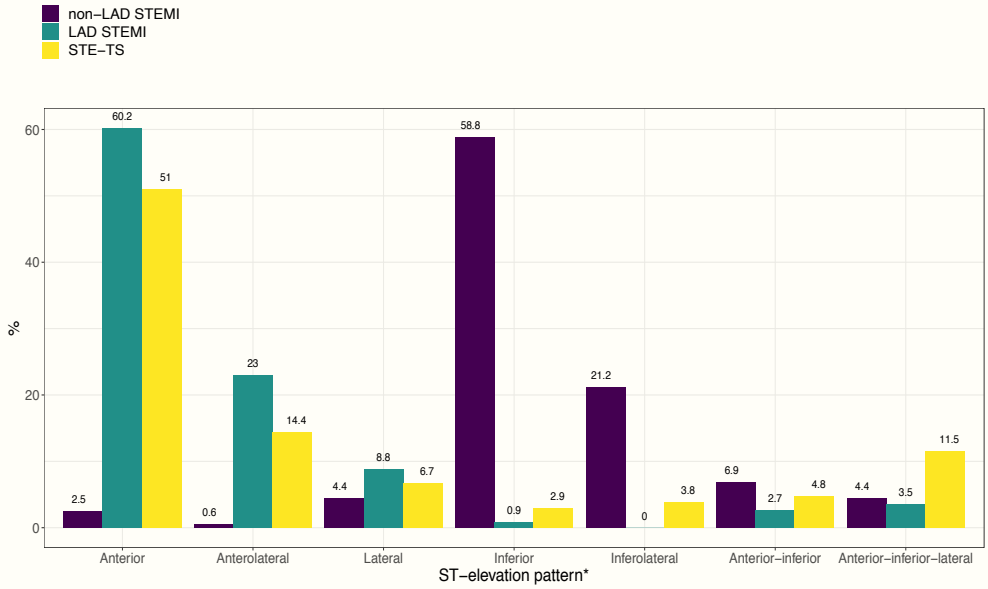


Figure 15. ST elevation pattern on admission. LAD = left anterior descending artery, STEMI = ST elevation myocardial infarction, STE-TS = ST elevation Takotsubo syndrome. Link to original: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9096129/ Used in accordance with CC BY 4.0: https://creativecommons.org/licences/by/4.0/

According to a significance level of $p < 0.05$, differences in ECG changes on admission in STE-TS versus LAD STEMI are summarized in table 6. We tested 23 different ECG variables, and with a Bonferroni corrected significance level of < 0.002, ST depression and reciprocal ST depression were the only non-lead-specific differences between STE-TS and LAD STEMI.

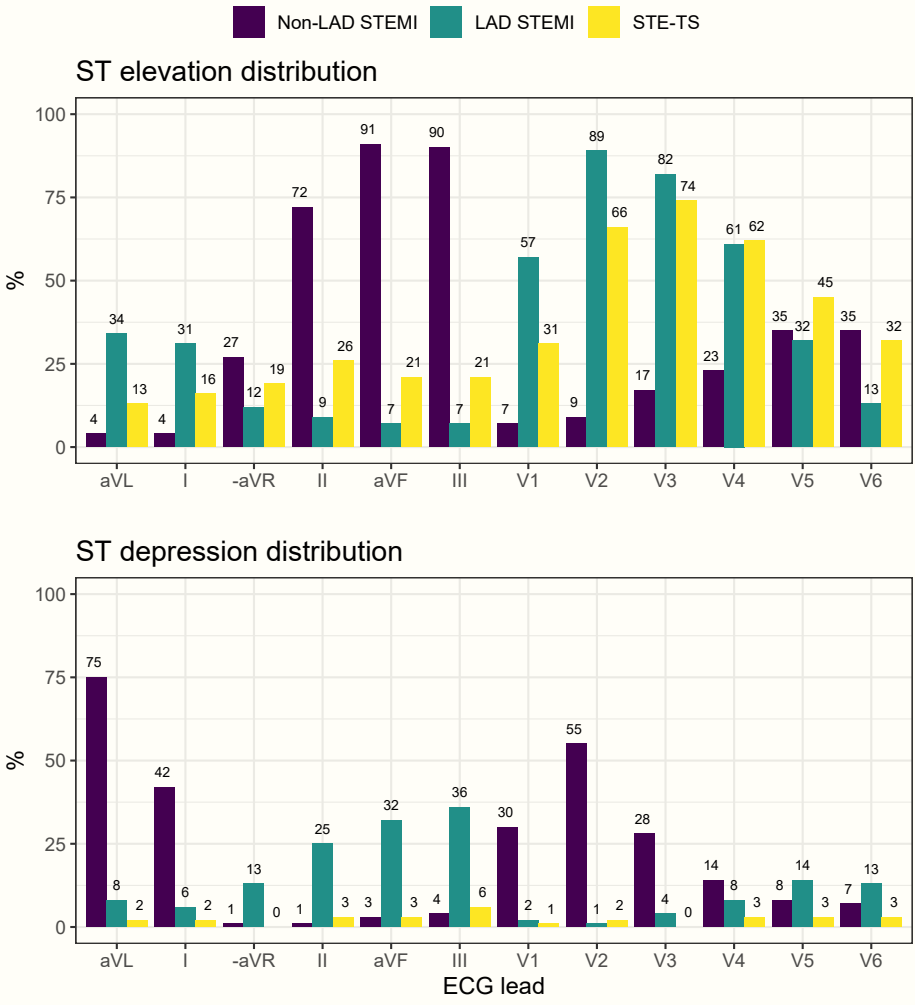


Figure 16. Lead-specific distribution of ST elevation and ST depression on admission. STEMI = ST elevation myocardial infarction, LAD = left anterior descending artery, STE-TS = ST elevation Takotsubo syndrome. Link to original: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9096129/ Used in accordance with CC BY 4.0: https://creativecommons.org/licences/by/4.0/

Table 6. Differences in ECG variables on admission between STE-TS and LAD STEMI. STE-TS = ST elevation takotsubo syndrome, LAD STEMI = left anterior descending artery ST elevation myocardial infarction. Bold p-values represents significant differences after Bonferroni correction.

Variable	STE-TS N = 104	LAD STEMI N = 113	p-value
PR interval	156 (140 – 172)	165 (146 – 186)	0.0058
QRS axis	25 (-27 – 68)	6.0 (-32 – 52)	0.040
T wave axis	69 (53 – 80)	48 (2.5 – 81)	0.0011
ST elevation with reciprocal ST depression	6.7% (7/104)	24% (27/113)	< 0.001
ST depression	9.6% (10/104)	37% (42/113)	< 0.001
Anterior-inferior-lateral ST elevation pattern	12% (12/104)	3.5% (4/113)	0.024

ST deviation magnitudes as predictors of LTVA or death

ST deviation magnitude predicted LTVA or death within 72 hours in LAD STEMI (the sum of all ST elevations and the sum of all ST deviations) and non-LAD STEMI (the sum of all ST deviations and the maximum single lead ST elevation), whereas none of the investigated ECG changes predicted LTVA or death in STE-TS.

3.5

STUDY IV

Study cohort

Study IV was a prospective study of ECG changes over time in female patients with TS and female and male patients with anterior STEMI. After informed consent, we enrolled adult patients (≥ 18 years old) with TS or anterior STEMI who were admitted to Sahlgrenska University Hospital from December 2019 to June 2022. Exclusion criteria were previous myocardial infarction or pre-existing persistent regional myocardial dysfunction; pacemaker rhythm on admission ECG and/or expected inability to comply with study protocol. Because of the low number of male patients with TS, these patients were excluded from the final analysis. All TS and STEMI diagnoses were confirmed according to ESC criteria [7, 44].

Screening of patients for inclusion

All patients with suspected STEMI (including TS patients presenting with ST elevation) in Gothenburg and parts of the region Västra Götaland are referred for immediate angiography (and if indicated primary PCI) at the cardiology department at Sahlgrenska University Hospital. The physicians responsible for the study are clinical physicians at the Cardiology Department of Sahlgrenska University Hospital. Therefore, all patients presenting with STEMI, and patients with TS presenting with ST elevation, during the referenced time period could be screened for eligibility for inclusion. Patients with TS presenting without ST elevation are routinely reported to the cardiology doctor on

call, enabling screening for eligibility. In cases where a TS patient was not reported to the cardiology department at presentation, screening was done at the time point of coronary angiography, leading to delayed enrolment for some patients with TS. However, since ECG is performed on admission irrespective of contact with the cardiology department, ECG was not delayed for this reason.

Data collection

12 lead ECGs were obtained in-hospital at the following time points: Admission (day 0), day 1 (24 ± 6 hours), day 2 (48 ± 12 hours), day 3 (72 ± 12 hours), day 7 (7 days ± 48 hours), day 14 (14 days ± 48 hours) and day 30 (30 days ± 48 hours). Baseline characteristics were obtained directly from patient anamnesis and/or from their medical charts. Clinical variables and results from diagnostic work-up were registered consecutively as patients were enrolled.

Method of ECG analysis

All 12-lead ECGs were recorded at a paper speed of 50 mm/s and an amplification of 10 mm/mV. Electronically derived values were used for PR interval, QRS duration, QRS axis and QT time. ST segment deviations were manually measured to the nearest 0.5 millimetre from the isoelectric line to the J-point for ST elevation, and to 60 milliseconds after the J-point for ST depression. T wave inversions were measured manually from the isoelectric line to nadir to the nearest 0.5 mm. The corrected QT interval (QTc) was calculated using Bazzet's formula. All ECGs were analysed and validated by two different physicians.

Endpoints and definitions

Anterior STEMI was defined as STEMI with culprit lesion in LAD or any of its branches. The primary endpoint/primary outcome variables were T wave inversion, the maximum single lead ST elevation and the average sum of all T wave inversions, from admission to day 30. The

secondary endpoints/secondary outcome variables were ST elevation, long QTc and pathological Q waves, from admission to day 30. The definitions of the primary and secondary outcome variables are summarized in Table 7. In this manuscript, the definition of T wave inversion from study I and II was redefined; from *T wave depth > 1 millimetre in any lead except V1* to *T wave depth > 1 mm in any two consecutive leads*. Also, the definition of long QTc in male patients was re-defined from *> 440 milliseconds* to *> 450 milliseconds*.

Table 7. Definition of outcome ECG variables in study IV.

Primary outcome variables	
T wave inversion	The proportion of patients with T wave inversion in percent (the number of patients with T wave inversion divided by the total number of patients within that group).
The maximum single lead T wave inversion	The depth of T wave inversion (in millimetres) in the lead with maximum depth of T wave inversion of all 12 leads.
Average sum of all T wave inversions	The sum of the absolute magnitude of T wave inversion in all 12 leads divided by 12.
Secondary outcome variables	
ST elevation	The proportion of patients with ST elevation in percent (the number of patients with ST elevation divided by the total number of patients within that group).
Long QTc	The proportion of patients with long QTc in percent (the number of patients with long QTc divided by the total number of patients within that group).
Pathological Q waves	The proportion of patients with pathological Q waves in percent (the number of patients with pathological Q waves divided by the total number of patients within that group).

Statistical analysis

Patients were categorized into female patients with TS, female patients with anterior STEMI or male patients with anterior STEMI. Standardized mean difference was used to assess balance of baseline characteristic between female patients with TS or anterior STEMI; as well as between female and male patients with anterior STEMI.

A mixed effects model (*lme4 package* in R) was used to test the difference in outcome variables between female patients with TS and anterior STEMI; as well as between female and male patients with anterior STEMI; from admission to day 30. All models (Models A, B and C) included group and day of ECG as fixed effects, and patient identification number (Patient ID) as a random effect; to account for the repeated measures design of the study. Model A was univariable without adjustment for baseline characteristics. Model B was adjusted for baseline characteristics; where age, hypertension, diabetes, chronic obstructive pulmonary disease and pre-admission treatment with beta-blockers were included as covariates. Model C was a univariable sensitivity model including only patients with complete ECG data (i.e. no missing ECGs) at day 0, 7 and 30 (N=82: 17 female TS, 23 female anterior STEMI, 42 male anterior STEMI). Possible interaction between group (disease type or sex respectively) and ECG day was tested before fitting the final models. All statistical analyses were performed using RStudio version 1.4.1717. The level of significance was set at $p < 0.05$.

Results

A total of 29 female patients with TS and 101 patients with anterior STEMI (31 female, 70 male) were included. Male anterior STEMI presented at the youngest age (64 ± 10 years old), followed by female TS (68 ± 9.8 years old) and female anterior STEMI (72 ± 12 years old). The median time from symptom onset to admission ECG was longest in female TS (127 [IQR 41 – 250] minutes), intermediate in female ante-

rior STEMI (99 [IQR 54 – 150] minutes) and shortest in male anterior STEMI (50 [IQR 29 – 100] minutes).

From day 0 to 30, there were no differences between female TS and female anterior STEMI; nor between female and male anterior STEMI; regarding T wave inversion, the maximum single lead T wave inversion or the average T wave inversion per lead. The odds of ST elevation was higher, whereas the odds of long QTc was lower, in female anterior STEMI compared with female TS. The odds of Q wave pathology was similar between female TS and female anterior STEMI. However, the odds of Q wave pathology was lower in female than male patients with anterior STEMI. (Figures 17-19, table 8)

In a post-hoc analysis (Figure 17 and 19 right hand side, Supplementary Table 1), only for patients with ECG recordings within 60 minutes from symptom onset (9 TS, 11 female and 34 male anterior STEMI) were investigated. In this analysis, there were no differences between the groups regarding ST elevation or any other variables, with the exception of the maximum single-lead T wave inversion which was larger in females than males with anterior STEMI.

N.B.: In the analysis of female TS versus female anterior STEMI with ECG recording within 60 minutes, the number of observations of ST elevation was low after day 3, resulting in extreme confidence intervals in the mixed model (marked as NA in Supplementary Table 1). Therefore, a non-mixed model (multivariable logistic regression) was used, excluding the random effect of patient identification number.

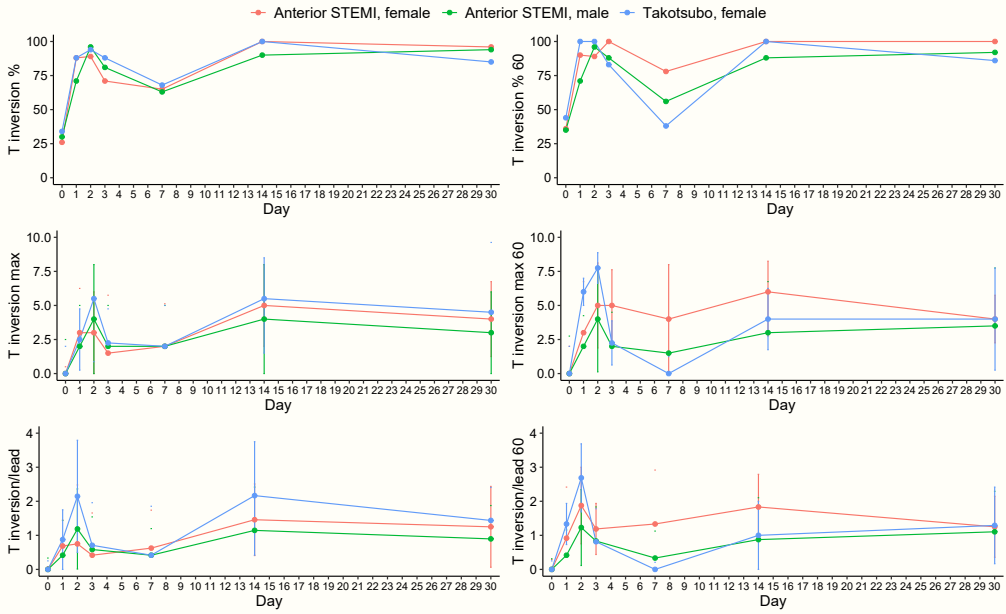


Figure 17. T wave inversion in temporal ECG analysis. T wave inversion from day 0 to 30 in all patients (left) and in patients with ECG recording within 60 minutes from symptom onset (right). STEMI = ST elevation myocardial infarction.

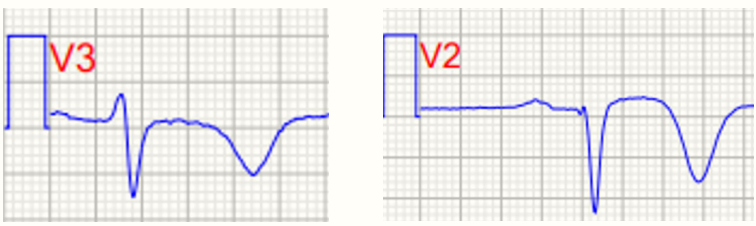


Figure 18. Examples of T wave inversion from study IV. Deeply inverted T wave in the sub-acute phases of TS (left) and anterior STEMI (right).

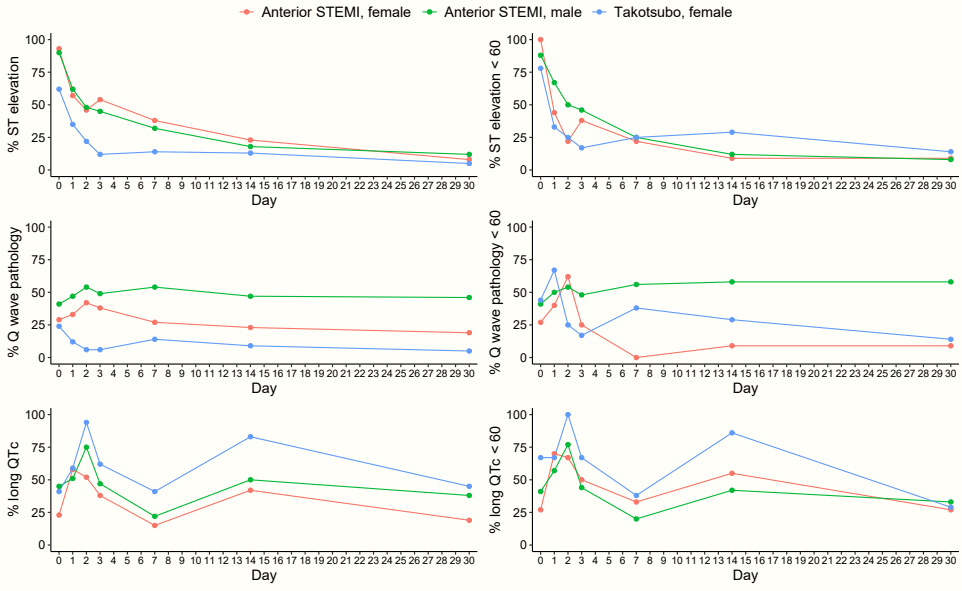


Figure 19. ST elevation, Q wave pathology and long QTc in temporal ECG analysis. ST elevation, Q wave pathology and long QTc from day 0 to 30 in all patients (left) and in patients with ECG recording within 60 minutes from symptom onset (right). STEMI = ST elevation myocardial infarction.

Table 8. ECG changes from day 0 to 30. *Univariable, †adjusted for age, hypertension, diabetes, chronic obstructive pulmonary disease and treatment with beta-blockers; ‡Sensitivity model only including patients with complete ECG data day 0, 7 and 30. STEMI = ST elevation myocardial infarction.

	Model A*	Model B†	Model C‡
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anterior STEMI versus Takotsubo syndrome, females			
T wave inversion (%)	0.81 (0.34 – 1.9)	1.1 (0.48 – 2.6)	1.1 (0.43 – 3.0)
Maximum T wave inversion (mm)	0.96 (0.39 – 2.4)	1.1 (0.42 – 2.9)	0.83 (0.31 – 2.2)
Average T wave inversion per lead (mm)	0.79 (0.57 – 1.1)	0.79 (0.57 – 1.1)	0.78 (0.55 – 1.1)
ST elevation (%)	8.1 (1.6 – 41)	5.7 (1.0 – 32)	9.3 (1.7 – 50)
Q wave pathology (%)	5.0 (1.0 – 25)	2.8 (0.57 – 14)	2.6 (0.50 – 13)
Long QTc (%)	0.22 (0.082 – 0.60)	0.27 (0.099 – 0.74)	0.18 (0.054 – 0.61)
Anterior STEMI, females versus males			
T wave inversion (%)	1.1 (0.56 – 2.2)	1.3 (0.64 – 2.8)	1.0 (0.49 – 2.2)
Maximum T wave inversion (mm)	1.4 (0.72 – 2.9)	2.1 (0.99 – 4.6)	1.2 (0.57 – 2.4)
Average T wave inversion per lead (mm)	1.1 (0.91 – 1.4)	1.3 (1.0 – 1.6)	1.1 (0.87 – 1.3)
ST elevation (%)	1.1 (0.23 – 5.5)	0.59 (0.11 – 3.3)	1.6 (0.52 – 5.1)
Q wave pathology (%)	0.29 (0.066 – 1.3)	0.19 (0.038 – 0.98)	0.18 (0.036 – 0.94)
Long QTc (%)	0.46 (0.18 – 1.2)	0.61 (0.21 – 1.8)	0.30 (0.079 – 1.2)

DISCUSSION

"Be able to defend your arguments in a rational way.
Otherwise, all you have is an opinion."

Marilyn vos Savant

4.1

METHODOLOGICAL CONSIDERATIONS

Although the analytical and statistical approaches used in this thesis are to be viewed as causal inference, the observational designs of study I-IV provide evidence only for association and not for cause. Also, due to the female predominance in TS, and the matching of patients by sex in study II and III (and the exclusion of male patients with TS in study IV), these results are mainly applicable to female patients with TS or STEMI. The most important methodological considerations per study are summarized below.

Study I

The VT variable in the composite primary endpoint of MACE included non-sustained and sustained VT. The significance of non-sustained VT (NSVT) after MI is debatable, as previous research shows no prognostic value of NSVT during the first 24 hours, whereas NSVT beyond this period is associated with increased in-hospital mortality [110]. The precise temporal significance of sustained versus non-sustained VT in

TS is not known, and our inclusion of NSVT in MACE was probably reasonable. However, a separation of sustained VT from NSVT would still have been preferable.

Table 1 contained a mix of baseline and ECG variables, where the baseline variables were not part of any hypothesis testing. According to professional statisticians, as well as according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology), significance testing should be avoided in descriptive tables (such as baseline characteristics tables) [111-113]. It may therefore have been more stringent to divide table 1 into two tables, one with baseline characteristics and one with ECG parameters. Regardless, the differences regarding all ECG parameters should be interpreted with caution, because of multiple statistical tests with increased risk of multiplicity and statistical type I error.

Strengths of this study included the large cohort relative to previous studies, the meticulous validation of all TS-diagnoses, and the comprehensive detailed ECG analysis. In addition, we likely obtained a good coverage of all arrhythmias, since arrhythmias were recorded in telemetry reports in all patients' medical charts three times per day (as part of clinical routine at the Cardiology Department of Sahlgrenska University Hospital).

Study II

We narrowed the time to the primary endpoint from "in-hospital" (study I) to within 72 hours in the present study, which is more specific and applicable to the recommended time for continuous monitoring of STEMI patients (at least 24 hours after symptom onset or longer for patients with risk factors) [44]. We also revised the primary endpoint from MACE (study I) to LTVA or death (study II), because *ventricular arrhythmia* or death was the endpoint of interest; and because the

definition of MACE is less uniform than that of LTVA. However, we did not register the cause of death which, in retrospect, would have been preferable.

When establishing a control group for the TS cohort, TS patients were age and sex matched 1:3 with STEMI patients from SCAAR. TS patients with matching pairs of anterior and non-anterior STEMI were subsequently included in the analysis. An alternative approach to matching may have been to match each TS patient against two anterior and two non-anterior STEMI patients directly from SCAAR (e.g. in a 1:2:2 manner). This may have resulted in a larger sample size of 1:1:1 matched patients with TS, anterior and non-anterior STEMI. However, at the time of data collection, we could not predict the number of STEMI patients where the diagnosis could not be validated, nor the exact number of missing triplets of TS, anterior and non-anterior STEMI.

Despite these considerations, the precise age- and sex-matching of patients with TS, anterior and non-anterior STEMI was a strength compared to previous studies. Other strengths were the detailed collection of data regarding arrhythmia; with separation of non-sustained from sustained VT; as well as the thorough validation of all STEMI diagnoses.

Study III

The occurrence of LTVA within 72 hours in study III was numerically lower in TS compared with STEMI, however, this difference was not statistically significant (1.9% versus 6.6%, $p = 0.072$). In study II, we found a lower occurrence of LTVA in TS compared with STEMI (0.6% versus 8.3%, $p = 0.0002$). Due to the small number of TS patients, study III was probably insufficiently powered to detect differences of outcome within the secondary endpoint (ECG predictors of LTVA or death within 72 hours).

We specified the sub-categories of STEMI as LAD and non-LAD STEMI in study III; in contrast to study II, were the sub-categories anterior and non-anterior STEMI were used. In study II, we used the interventional cardiologist's summarized assessment of infarct localization, whereas we registered the specific segments of all culprit lesions in study III. Therefore, the definition of infarct localization was more precise in study III compared with study II. Also, we believed specifying STEMI as LAD or non-LAD STEMI (instead of anterior or non-anterior) was clearer to the reader.

The cohort in study III was a sample from our matched cohort of TS and STEMI patients from studies I and II, including only patients presenting with ST elevation (STE-TS versus STEMI). The number of STEMI patients was restricted because a proportion of these patients did not have a matching patient with STE-TS. An alternative approach would have been to match all TS patients presenting with ST elevation to patients with STEMI directly from SCAAR. That said, the cohort of patients with STE-TS or STEMI achieved good balance on the matching variables age and sex. Also, the number of STEMI patients; and the overall size of the cohort; was larger compared with most previous studies, and constituted a strength relative to previous research. Therefore, we decided that the quality of the matching process was acceptable for investigating the primary endpoint.

As in study I, the multiple comparisons of ECG parameters in study III increased the risk of multiplicity and statistical type I error. Although we did not adjust the significance level per se in the published manuscript from study III, the differences emphasized were large. In the present thesis, a Bonferroni adjusted significance level was applied as described above.

Study IV

In contrast to study I-III, study IV was a prospective study with consecutive enrolment of patients with TS or STEMI. Therefore, the sample size of study IV was smaller than studies I to III. Study IV was a sub-study in the multi-centre STAMI project. In the original study design, and according to the original ethical approval, enrolment of patients for 1 ½ years was planned (original ethical registration number 2019-04092). This was extended in later ethical approvals (registry numbers 2020-06257 and 2021-01921). For the ECG part of this project, we extended the inclusion of patients to 2 ½ years; to obtain a larger sample size and more statistical power. Still, the small sample size is a limitation of this study, and the risk of statistical type II error must be kept in mind when interpreting the results.

We did not include male patients with TS in the final analysis of study IV. This was a limitation making the results are less generalizable to male patients with TS. Instead of matching patients according to age and sex, the patients in study IV were stratified according to sex, where the number of male TS patients was too small to provide basis for any meaningful statistical analysis. Naturally, the groups in study IV were less balanced with respect to age, compared to study II and III. However, age was included as a covariate in the outcome analysis in Model B in study IV.

Strengths of study IV included the prospective design; the detailed information regarding times from symptom onset to ECG as well as between ECGs; the detailed ECG analyses, and the temporal head-to-head comparisons between TS and anterior STEMI. Also, none of the included patients had experienced previous myocardial infarction nor had pre-existing regional cardiac dysfunction, which is a major strength compared with previous research. Lastly, although admission ECG was only missing for one patient, 18-29% of patients had missing follow-up

ECGs depending on day. However, the statistical model used (mixed effects model) is capable of handling missing data under the *missing at random* assumption.

4.2

MAIN FINDINGS IN SHORT

In study I, the major finding was that T wave inversion on admission ECG was associated with lower risk of in-hospital MACE in TS. Also, study I provided detailed information of ECG and outcome in TS which was subsequently compared to STEMI in study II and III. In study III, the main finding was that admission ECG in TS was considerably more similar to STEMI with culprit coronary occlusion in LAD compared with a non-LAD vessel, which is in accordance with previous research showing ECG similarities between TS and *anterior* STEMI specifically [14, 114]. In study IV, the similarities of ECG in general, and of T wave inversion in particular, between TS and STEMI were further emphasized through comparison of temporal ECG from admission to day 30. Although the approach of this thesis was to identify differences to separate ECG in TS from STEMI, the results rather highlighted the similarities between the two conditions.

In study II, we found a considerably lower risk of LTVA (despite similar or greater severity of AHF in TS), but similar risk of all-cause mortality, within 72 hours from admission in TS compared with STEMI. In recent

years, increasing attention has been paid to observed similarities in *outcome* (including arrhythmia and mortality) between TS and AMI/STEMI [7, 14, 99]. However, there are several aspects to keep in mind when comparing outcome in TS to STEMI. The results from study I-IV regarding ECG, LTVA and mortality in TS versus STEMI, as well as pathophysiological implications of these findings, will be further discussed below.

4.3

ELECTROCARDIOGRAPHY

Admission ECG

ECG on admission in STE-TS was considerably more similar to LAD than non-LAD STEMI in study III, and no ECG criteria were found to separate STE-TS from LAD STEMI. With a Bonferroni corrected significance level, ST depression and reciprocal ST depression were the only non-lead-specific differences between STE-TS and LAD STEMI. This is in accordance with previous literature and a meta-analysis showing that absence of reciprocal ST depression was the only ECG change associated with TS in comparison to anterior STEMI [14, 115].

The similarities between STE-TS and LAD STEMI remained in the lead-specific analysis of study III. The only ***distinct*** lead-specific difference was that STE-TS presented with inferior *ST elevation*s (1 of 4 patients), whereas LAD STEMI presented with inferior ST *depressions*

(1 of 3 patients). This observation, together with the rarity of reciprocal ST depression in TS, indicate a more diffuse, "symmetrical" and widespread distribution of ECG changes in TS compared with STEMI; corresponding to the typical wall-motion abnormalities in TS. As far as we know, the role of inferior ST elevations for separating TS from anterior STEMI has only been emphasized once before [116], where study III adds a novel aspect through supplying the most detailed lead-specific comparison between STE-TS and STEMI to date.

Temporal ECG

In study IV, the main finding was that the development of T wave inversion (proportion of T wave inversion, maximum single lead T wave inversion and the average T wave inversion per lead) from admission to day 30 was similar in female patients with TS and anterior STEMI. In contrast to the previous notion that deep, widespread and persistent T wave inversions are "TS-typical", this may indicate that T wave inversion is more similar in TS and STEMI than previously thought [14, 117-119].

The timing of ECG was carefully addressed in study IV, because systematic delay in any of the groups will lead to un-synchronized comparisons. In previous retrospective analyses, comparing TS with anterior STEMI and LAD ACS respectively, more widespread T wave inversions was seen in TS. However, none of these studies stated time from symptom to admission ECG, nor the time between ECGs [118, 119]. A prospective study, with head-to-head comparison of ECG in TS and a mixed population of anterior and non-anterior STEMI, showed more T wave inversion by day 2 in TS. Again, this study did not specify time from symptom to ECG, nor the time elapsed between ECGs [117].

ECG changes follow the temporal phases of TS, where the presence of ST elevation is an early ECG change [120]. In study IV, patients with ECG recording within 60 minutes from symptom onset, 78% (7/9) had

ST elevation on admission compared with 62% (18/29) overall. In temporal analysis, although ST elevation was less common in TS compared with STEMI overall, there was no difference in ST elevation in patients with ECG recordings within 60 minutes. Although this subset of patients was small, this further supports that the presence of ST elevation reflects the acute phase of TS, whereas T wave inversion is a sub-acute sign [120].

According to previous research, dynamic precordial T wave inversion accompanied by QT prolongation may be a manifestation of the Wellen's ECG pattern in both TS and AMI/STEMI [87, 121]. Wellen's ECG pattern has traditionally been viewed as unfavourable, because of its association with untreated critical stenosis and sub-occlusion of LAD [122]. However, in re-perfused STEMI, transient T wave inversion/QT prolongation has been reported as a favourable sign, associated with stunned viable myocardium and smaller infarct size [123-126]. In study IV, we observed that T wave inversion was accompanied by QT prolongation (in a dynamic biphasic temporal pattern) in both TS and anterior STEMI. Thus, the observations in study IV supports the presence of Wellen's ECG pattern (perhaps as related to myocardial stunning) in both TS and STEMI.

Although the occurrence of T wave inversion was similar in study IV, QT prolongation was more common in female TS compared with female anterior STEMI, which is accordance with previous research [14]. Conversely, the odds of Q wave pathology in study IV was nominally lower in TS compared with female anterior STEMI, and significantly lower compared with male anterior STEMI. Whereas Q wave pathology has been linked to myocardial necrosis [63] (or stunning if transient [60, 120]), CMR studies have proposed that myocardial oedema may be the substrate for dynamic T wave inversion *and* QT prolongation (Wellen's ECG pattern) [121, 127]. In fact, oedema in viable myocardium may be an

early ischemic sign preceding infarction in STEMI [128]. As opposed to partly infarcted tissue in STEMI, a purely stunned myocardium in TS; with prolonged depolarization action potential due to oedema rather than electrical inactivity due to necrosis [52]; may theoretically explain more QT prolongation in TS compared with STEMI. Also, myocardial stunning as opposed to infarction may explain less Q wave pathology in TS compared with STEMI.

The proportion of patients with T wave inversion versus QT prolongation in Figures 17 and 19 indicate that some patients with TS or STEMI had T wave inversion *without* QT prolongation. The QT interval reflects *depolarization* whereas the T wave reflects *repolarization* [52], which may indicate that repolarization abnormalities persist after resolution of depolarization abnormalities in both conditions.

4.4

LIFE-THREATENING VENTRICULAR ARRHYTHMIA

A larger infarct size and persistent ischemia is associated with increased risk of arrhythmia in STEMI [129, 130], whereas signs of myocardial infarction is generally absent in TS [14], which probably explains the low occurrence of LTVA in TS compared with STEMI in study II.

The reported occurrence of in-hospital LTVA in TS varies widely in previous literature. Since TS is associated with other serious medical

conditions (such as sepsis, cerebral haemorrhage, acute respiratory disease and treatment for cardiac arrest) [14], a representable selection of patients is important to obtain the true occurrence of LTVA in TS. Also, different *definitions* of LTVA will affect the reported occurrence. Studies including NSVT (non-sustained ventricular tachycardia) in LTVA [72, 131], and studies of cohorts with a large proportion of serious co-existing disease [78], has reported the highest occurrence of in-hospital LTVA in TS (13.5%, 11.4% and 10.7% respectively). Larger studies, as well as studies not including NSVT in LTVA and with less co-existing disease, has reported lower occurrence of in-hospital LTVA in TS (around 3%) [11, 73, 132, 133].

In studies I-III, any VT/VF (non-sustained or sustained VT or VF) occurred in TS in 20 of 215 (9.3%), 19 of 155 (12%) and 11 of 104 (11%) patients respectively. The previously mentioned studies including NSVT in LTVA [72, 131], showed similar occurrence of any VT/VF (13.5% and 11.4%) as in studies I-III. Thus, including NSVT in LTVA may overestimate the occurrence of severe arrhythmia in TS, and should therefore probably be avoided.

In study II, LTVA (only sustained VT or VF) occurred in only 1 of 155 (0.6%) patients with TS. In contrast, one previous study (also excluding NSVT from LTVA), reported 10.7% occurrence of in-hospital LTVA in TS [78]. However, in this previous study 10 of 214 (4.7%) patients presented with cardiac arrest, compared with only 2 of 155 (1.3%) patients in study II. Among the 10 patients presenting with cardiac arrest in the previous study, it is hard to establish if TS was a cause or consequence of cardiac arrest, and the occurrence of LTVA *caused* by TS may have been overestimated. The largest study to date (N=16450) of in-hospital arrhythmias in TS showed 3.6% occurrence of any VT and 1.0% occurrence of VF, which is similar to our results from study II.

With reference to the above, and to compiled numbers of arrhythmia in TS, the true occurrence of LTVA in TS may be around 1-3% [73, 132, 133]. If this estimation of LTVA in TS is correct, the occurrence of LTVA is nominally lower in TS compared with STEMI (3-6% following intervention) [44, 83]. This is consistent with our results from study II, with a lower risk of LTVA in TS compared with STEMI.

4.5

MORTALITY

In study I, 10 of 215 patients (4.6%) with TS died in-hospital, which is in accordance with a meta-analysis from 2014 showing 4.5% in-hospital mortality in TS. In the two samples of TS patients in study II and III, the occurrence of death within 72 hours was 1.9% (3/155) and 4.8% (5/104) respectively. The different selection and small sample sizes may explain the difference of mortality in TS between study II and III, where only a few patients affect the overall percentage. The different time to the endpoint (in-hospital in study I and within 72 hours in studies II and III) may explain the higher mortality in TS in study I compared to study II. The lower mortality of TS study II than study III may hypothetically be explained by earlier presentation to hospital in study III, which may be associated with more severe disease. In this scenario, the earlier presentation of TS patients in study III (only TS with ST elevation) is based on ST elevation as an early ECG sign in TS [120].

When comparing mortality between TS and STEMI, death from any cause within 72 hours was similar (studies II and III). Two large previous studies from SCAAR demonstrated similar mortality in TS and AMI/STEMI [134, 135], which is in accordance with our results. As a sequel to one of these previous studies [135], a large nationwide Swedish study from the same registry showed that 30-day mortality in TS was higher compared with NSTEMI, but lower compared with STEMI [99]. Although these similarities in mortality in TS and AMI have been emphasized in recent years [14], non-registry studies with head-to-head comparisons of outcome have shown lower in-hospital mortality in TS compared with both NSTEMI and STEMI [102, 103].

Registry studies in general cannot handle the issue of wrong diagnosis and/or wrong coding [104]. Since a hallmark of TS is the close similarity to AMI [14, 136], correct TS diagnosis is crucial for obtaining representable comparisons between the two conditions. If the diagnosis cannot be verified, the risk of including AMI patients in the TS group is high, which may result in a proportion of the comparisons being AMI versus AMI. This would lead to *differential* misclassification of exposure, since the risk of misdiagnosing TS patients is probably higher than that of AMI patients, with reference to TS likely being underdiagnosed [137, 138]. In the setting of comparing TS to AMI, such a misclassification may lead to bias overestimating the similarities between the two conditions.

In contrast to registry studies, observational studies (such as study II and III in the present thesis) allow validation the TS and AMI diagnoses, eliminating bias from misclassification of exposure. Regardless, results regarding mortality in TS are somewhat conflicting both between different observational studies [100, 102, 103] and between different registry studies [99, 134]. However, the largest discrepancies between *observational* studies are regarding *long-term* mortality, whereas most

of these studies show similar or lower *short-term* mortality in TS compared with STEMI [100, 102, 103].

It is important to note that all of the above-mentioned studies investigated *all-cause* mortality, and not *cardiac-specific* mortality. Research addressing both cardiac and non-cardiac mortality has demonstrated lower in-hospital cardiac mortality in TS compared with AMI [139]. Although one study showed similar *cardiovascular* mortality in TS and STEMI, this study included both cardiac (myocardial infarction, heart failure, arrhythmia or sudden cardiac death) and non-cardiac (cerebrovascular disease, pulmonary embolism or "other vascular diseases") conditions as "cardiovascular death" [100]. In the present thesis, cardiac-specific mortality was not investigated.

In the above-mentioned meta-analysis, the in-hospital mortality of primary TS (not triggered by underlying physical illness) was found to be as low as 1.0%. [104]. Accordingly, a large proportion of the mortality in TS is related to underlying non-cardiac illness, and more so in TS compared with AMI [82, 104, 139]. TS is a complicating factor for patients with critical illness [7, 14, 104], and the non-cardiac mortality in TS should not be overlooked. However, in-hospital mortality in TS without underlying critical illness is likely low [104], and should therefore be separated from TS with underlying critical illness when comparing in-hospital mortality between TS and AMI.

4.6

ELECTROCARDIOGRAPHIC PREDICTORS OF OUTCOME

In TS, we found a lower risk of in-hospital MACE associated with T wave inversion (study I) which is consisted with findings in AMI, where transient early negative T waves after reperfusion after AMI has been described as marker of improved 30-day and in-hospital survival respectively [140, 141]. These observations are also in accordance with T wave inversion/Wellen's ECG pattern as a sign of viable stunned myocardium and favourable outcome in re-perfused STEMI (in contrast to un-treated sub-occlusive LAD stenosis) [123-126, 140, 141]. In TS, as opposed to re-perfused STEMI, all mechanical dysfunction is thought to be caused by myocardial stunning per se [5], regardless of T wave inversion. Therefore, stunning per se does not provide a pathophysiological basis for T wave inversion as a marker of favourable outcome in TS. However, T wave inversion may be associated with faster recovery of stunning in TS, which is covered later under section 4.8.

In study III, ST deviation magnitudes (the sum of all ST elevations/deviations and maximum single-lead ST elevation) were associated with LTVA or death within 72 hours in STEMI but not in STE-TS, which is in accordance with previous literature regarding STEMI [130]. In one previous study with a composite endpoint consisting of seven clinical variables, the sum of all ST elevations predicted "complications" in TS [142], but the association with LTVA or death has not been previously investigated. The transient nature of ST segment changes in TS may

point towards faster resolution of the pathophysiological substrate in TS compared with STEMI. Indeed, for believers of ischemic pathophysiology in TS, the perfusion defects observed in TS have been transient as opposed to STEMI [143].

Regardless of the pathophysiology, ECG changes reflect the temporal phase of TS [14]. Therefore, the resolution of ST elevation may precede the first ECG recording on admission [120], also pointing towards reversible underlying mechanisms affecting myocardial tissue. In STEMI, ST segment changes are more persistent compared with TS (as shown in figure 15) and a larger infarct size is associated with more arrhythmia and worse outcome [129, 144]. The transition from myocardial ischemia to infarction in STEMI; and the transition from myocardial stunning to complete recovery in TS; probably explains the predictive value of ST segment changes in STEMI as opposed to TS.

4.7

ACUTE HEART FAILURE

In both TS and STEMI, the extent of left ventricular dysfunction and AHF are predictors of poor outcome [14, 44]. However, a dissociation between clinical signs of AHF and cardiac dysfunction in TS has previously been described [12, 13], for which the pathophysiological basis in unclear. This is in accordance with our results from study II, where patients with TS had a lower risk of LTVA compared with STEMI, de-

spite similar or greater severity of AHF. This dissociation is not seen in STEMI, were cardiac dysfunction generally corresponds to clinical heart failure; and where persistent cardiac dysfunction and cardiogenic shock may lead to progressive multiple organ failure [44, 145]. Although cardiogenic shock occurs as a complication in TS as well, most patients spontaneously recover cardiac function within days to weeks [5]. The overall pathophysiological compensatory response to AHF is adaptive at first, but becomes maladaptive over time [146]. Hypothetically, in contrast to severe AHF caused by STEMI, the transient nature of cardiac dysfunction in TS may allow the adaptive pathophysiological response to AHF/cardiogenic shock to evert deterioration to multiple organ failure.

4.8

PERSPECTIVES ON THE PATHOPHYSIOLOGY OF TAKOTSUBO SYNDROME

Pathophysiologic perspectives on ECG changes

From an electrophysiological perspective, transmural ischemia causes localized ST elevation (STEMI) and subendocardial ischemia causes diffuse ST depression (as in NSTEMI if caused by coronary artery stenosis) [47, 51-53, 63, 147, 148]. In accordance with previous literature, ST elevation was common in TS in the studies included in this thesis, whereas ST depression was rare [5, 60, 120]. The similarity of ECG in TS and anterior/LAD STEMI in general, and the presence of ST ele-

vation/rarity of ST depression in TS in particular, may point towards transmural ischemia playing a role in the pathophysiology of both conditions. The absence of ST elevation in a proportion of TS patients may be explained by delayed presentation [120], which is in accordance with our finding from study IV, where ST elevation was more common in TS (and similar to STEMI) closer to symptom onset.

The main ECG difference found in study III and IV was the low proportion of reciprocal ST depression in TS compared with LAD/anterior STEMI. Although reciprocal ST depression is a sign of transmural ischemia in the setting of STEMI [149], the absence of reciprocal ST depression in TS does not contradict possible transmural ischemia. Regardless if reciprocal ST depression is a mirror phenomenon [68-70], or a sign of multivessel disease [149] (or a combination of both), none of those circumstances are applicable to TS. The extensive wall-motion abnormality in TS may eliminate the prerequisites for having affected and non-affected myocardium in opposite parts of the heart, and multivessel disease as a cause of ECG changes in TS is by definition excluded.

It has been proposed that precordial T wave inversion/QT prolongation (Wellen's ECG pattern) is an electrophysiological correlate of myocardial stunning/viable myocardium [124, 126]. This may correspond to the initial increase (day 1–2) and decrease (day 2/3–7) of T wave inversion/QT prolongation in TS (and STEMI) in study IV, since myocardial stunning is an early phenomenon. Serial evaluations in TS have revealed rapid resolution of stunning with recovery of systolic function the acute and subacute phase, where most of the systolic function was recovered within the first days [5, 17, 150, 151]. However, T wave inversion/QT prolongation re-occurred day 7-14 and decreased again day 14–30 in study IV. QT prolongation was present in almost half of patients, and T wave inversion persisted in almost all patients, at day 30. Myocardial oedema

persists longer than stunning [14], and CMR studies have shown transmural myocardial oedema in both TS and STEMI [74, 87, 152], which in turn has been associated with Wellen's pattern [87, 121]. Therefore, Wellen's ECG pattern is probably a manifestation of myocardial oedema, which in turn may be caused by ischemia with post-ischemic stunning at some point in both TS and STEMI [87, 121, 153].

As covered above, T wave inversion/QT prolongation followed a biphasic temporal evolution in both TS and STEMI in study IV, which corresponds to transient normalization of T waves and shortening of the QT interval in a proportion of patients. Although such paradoxical normalization (pseudo-normalization) has been observed in TS previously, the pathophysiological cause is unknown [154, 155]. However, pseudo-normalization of inverted T waves also occurs in acute ischemia [52, 156-158], and late reperfusion with subsequent recurrence of ischemia is therefore a hypothetical explanation for the pseudo-normalization observed in study IV (Figure 20). A biphasic temporal pattern of myocardial oedema has been demonstrated with CMR after I/R in pigs, where reperfusion-injury is thought to cause the initial peak of oedema, whereas the cause of the second peak is unknown [159, 160]. Hypothetically, the initial T wave inversion/QT prolongation may be associated with oedema with varying degree of I/R injury [121], whereas pseudo-normalization may be caused by recurrence of ischemia/re-stunning, perhaps secondary to microvascular injury; which previously has been observed in patients with late reperfusion [160]. Since STEMI patients in study IV where re-perfused (and TS patients had no coronary obstruction) on the epicardial level, such supposed recurrence of ischemia would be assumed to occur at the microvascular level, which is also applicable to TS (according to the microvascular pathophysiological theory) [33-35].

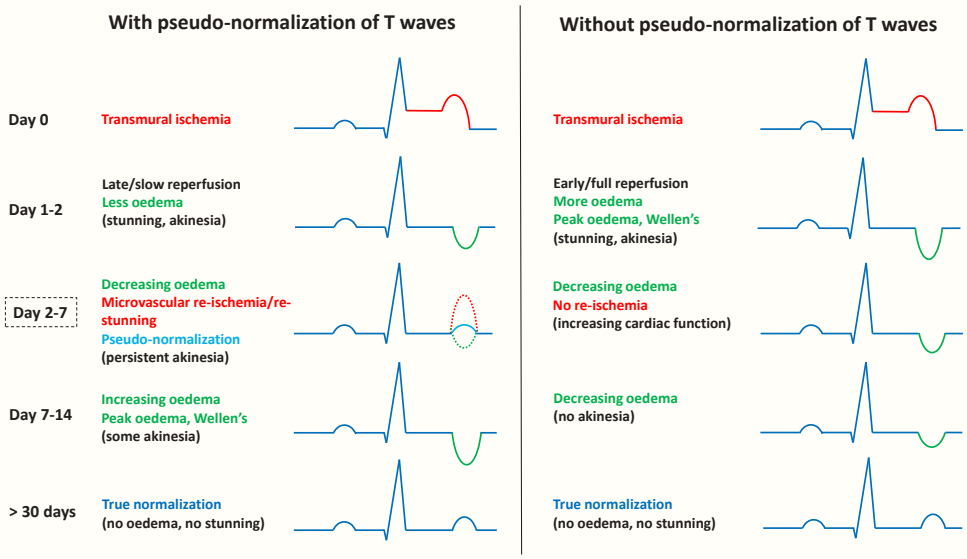


Figure 20. Theory of pseudo-normalization of T waves in TS and STEMI.

In post-hoc analysis, resolution of ST elevation flattened out corresponding to the time period of pseudo-normalization of T waves and shortening of the QT interval. Nominally, ST elevation *increased* in patients with pseudo-normalization, but *decreased* in patients without pseudo-normalization (all patients included, TS and STEMI), from day 2 to 3 (Figure 21, Supplementary Table 2 and Supplementary Figure 1). This may indicate persistent/recurrent ischemia in both TS and STEMI patients with pseudo-normalization of T wave inversion and QT prolongation.

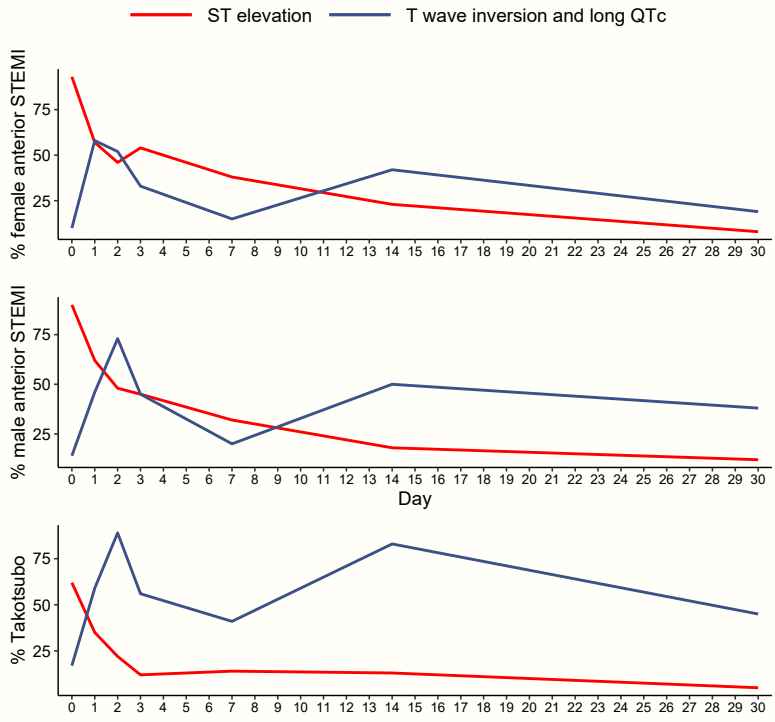


Figure 21. Figure. ST elevation and the composite of T wave inversion and long QTc from day 0 to 30. The temporal pattern of ST elevation and the composite of T wave inversion and long corrected QT interval (long QTc) in female patients with anterior ST elevation myocardial infarction (STEMI) and female patients with Takotsubo syndrome (TS).

Although the temporal pattern of wall-motion abnormality was not investigated in the present thesis, the pseudo-normalization of T waves observed in study IV corresponds to the time period when many, but not all, patients recover their cardiac function [150, 151]. Although hypothetical, if pseudo-normalization of inverted T waves was associated with recurrence of ischemia, this may lead to "re-stunning", with prolonged recovery as the expected consequence. Conversely, persistent negative T waves without pseudo-normalization may be associated with early resolution of stunning. This would correspond to our results from

study I, where T inversion was associated with a lower risk of in-hospital MACE.

Pathophysiologic perspectives on ventricular arrhythmia

Hypothetically, if transient ischemia because of microvascular dysfunction/spasm plays a role in the pathophysiology of TS, the occurrence of NSVT in TS may be a manifestation of "reperfusion-arrhythmia". In relation to ***sustained*** VT, we observed a higher occurrence of NSVT in TS in studies II and III (0% versus 12% and 1.0% versus 8.6% respectively). In Prinzmetal/variant angina, where vasospasm (in epicardial arteries as opposed to the microcirculation) is thought to be the primary cause of ischemia, reperfusion-arrhythmia is also seen, where the duration of vasospasm is determines the severity of arrhythmia [161]. Reperfusion-arrhythmia (with frequent short burst of NSVT) are also common in re-perfused STEMI [110], which is in accordance with our results where NSVT was common in STEMI (37% and 38% in studies II and III respectively).

Microvascular dysfunction and transient ischemia as a possible cause of TS

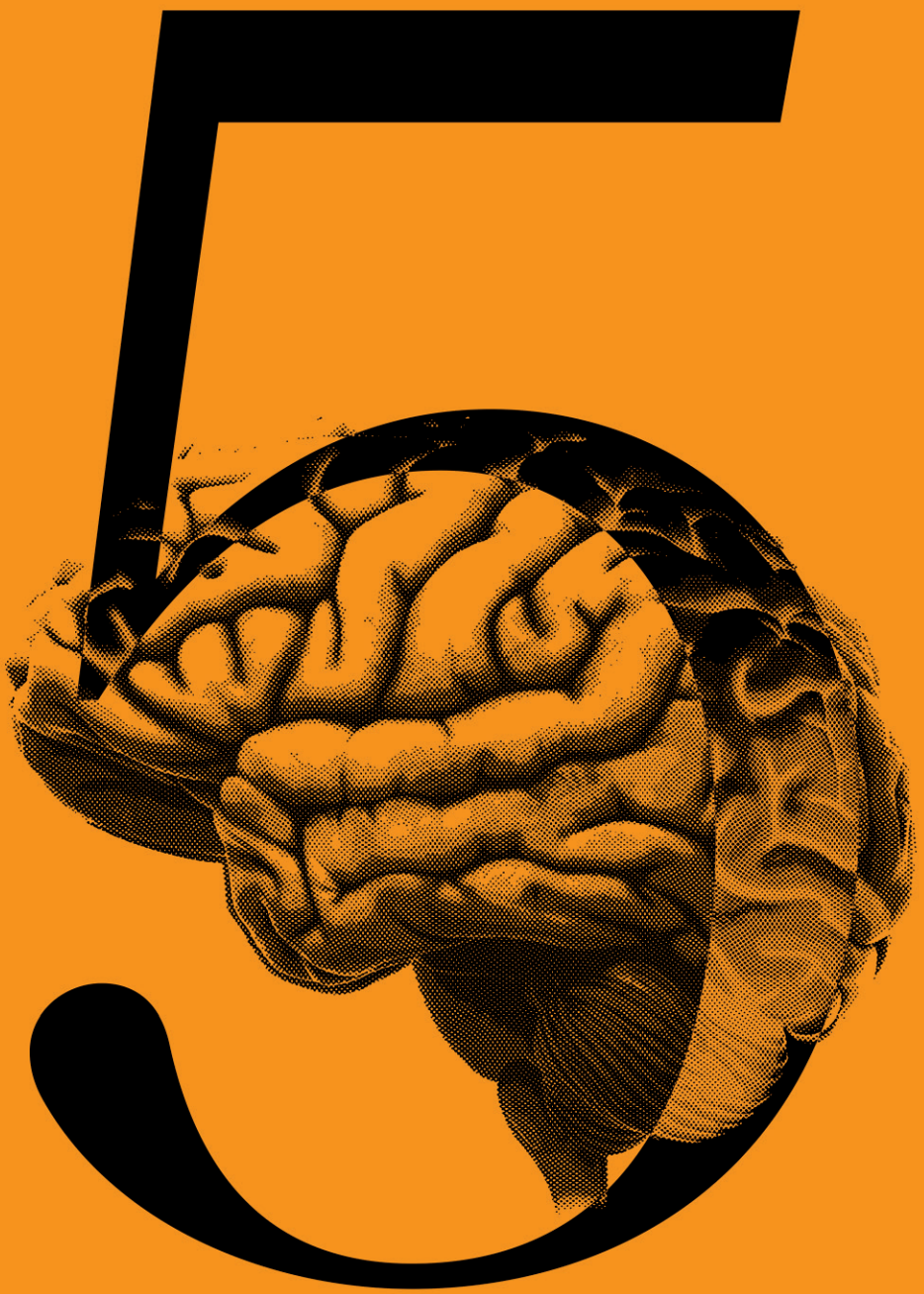
Based on the electrophysiological basis for ECG changes, with STEMI as the pathophysiological reference, the ECG pattern in TS observed in the present thesis may be interpreted as "transient ischemic". Also, the likely presence of Wellen's ECG pattern in both TS and STEMI, may indicate transmural ischemia and transmural oedema in both conditions. As mentioned above, myocardial oedema has been demonstrated as an early sign of transmural ischemia, preceding myocardial infarction [128]. Except for the ECG similarities, as well as the overall similarities between TS and AMI/STEMI [5,14], there are also common denominators regarding histopathological and radiological findings in TSand STEMI.

A distinct and well-established histopathological finding after myocardial I/R injury (after PCI or transient vasospasm) is contraction band necrosis (hypercontracted cardiomyocytes) which can be observed as early as within minutes after reperfusion [162-164]. Interestingly, contraction band necrosis is also the typical histopathological finding in TS [5, 17]. Although generally regarded as absent in TS, late gadolinium enhancement (as is a marker of myocardial injury/infarction on CMR), has been observed in a minority of TS patients according to previous research. However, the finding of late gadolinium enhancement was much less pronounced compared with what is generally seen in AMI/STEMI [87]. Consequently, there are histopathological and radiological observations related to I/R injury in both TS and STEMI, which may correspond a transient ischemic ECG pattern and reperfusion-arrhythmia.

Microvascular disturbances in TS, including diffuse impairment of myocardial perfusion and slow blood-flow in regions of the heart corresponding to segments with mechanical dysfunction, have been demonstrated through both invasive and non-invasive methods in numerous studies [143, 165]. Diffuse transmural ischemia and impairment of myocardial perfusion may correspond to the diffuse distribution of ST elevation seen in study III. In addition, slow-flow in diverse coronary artery territories, with a greater impairment of coronary flow in the LAD area, has been observed in patients with TS. This is a possible explanation for the apical regions being more severely affected in TS [143, 166], which may correspond to the finding in study III that ECG in TS was especially similar to LAD STEMI.

Microvascular angina [33] and TS [5] are more common in women compared with men, in contrast to IHD which develops later in women compared with men [44]. This may indicate a larger role of microvascular dysfunction in women compared with men [58, 59], corresponding to the female pre-dominance in TS. Studies comparing TS and STEMI

have shown strictly microvascular dysfunction in TS as opposed to STEMI [34]. Regarding the pathophysiological substrate for microcirculatory dysfunction, previous studies have provided some evidence for endothelial dysfunction, microvascular dysfunction and microcirculatory spasm, in patients with TS [33, 167].



CONCLUSION

"Nature's music is never over; her silences are pauses,
not conclusions."

Mary Webb

ECG changes on admission, and from admission to day 30, were similar in TS and anterior/LAD STEMI. No ECG criteria to distinguish the two conditions was found, and coronary angiography is still mandatory to exclude coronary artery occlusion. The risk of LTVA or death within 72 hours from admission was lower in TS compared with STEMI (driven by a lower risk of LTVA) despite similar or higher degree of AHF in TS. ST deviation magnitude predicted LTVA or death within 72 hours in STEMI, but not in STE-TS. The only ECG predictor of outcome in TS was T wave inversion on admission, which was associated with a lower risk of in-hospital MACE.

Although ECG was similar in TS and LAD/anterior STEMI, some differences were identified. ST depression and reciprocal ST depression were less common on admission in TS compared with LAD STEMI. In temporal analysis, long QTc was more common, whereas ST elevation was less common, in TS compared with STEMI. However, for patients with ECG recordings within 60 minutes from symptom onset, these ECG changes were similar between the two conditions.

In literature dating back to the first years of the 21th century, repeated attempts have been made to distinguish TS from AMI/STEMI through early non-invasive diagnostic tools such as ECG [11, 14, 60, 117, 136, 168-171]. If anything, the present thesis demonstrated a conspicuous resemblance of ECG in TS and anterior/LAD STEMI. Distinguishing TS from AMI/STEMI is essential, because of the possible detrimental effects for TS patients receiving hazardous treatment without indication, as well as for the dangers of missing a coronary occlusion in a patient with STEMI. Therefore, separating the two conditions based on ECG may not be feasible. However, ECG may provide important clues regarding the outcome or pathophysiology of TS.

With STEMI as the pathophysiological reference, temporal ECG in TS may be interpreted as following a "transient ischemic pattern". The presence of ST elevation and rarity of ST depression may indicate *diffuse* transmural ischemia in TS, and Wellen's ECG pattern and pseudo-normalization of T waves may indicate microvascular re-ischemia/re-stunning in both conditions. The diffuse distribution of coronary microvasculature may explain the diffuse ECG changes in TS, as opposed to the localized ECG changes in STEMI. Together with common denominators regarding radiological and histopathological findings, this may indicate that transmural ischemia occurs in both TS and STEMI.

CLOSING REMARKS AND FUTURE PERSPECTIVES

"Humans are allergic to change. They love to say, 'We've always done it this way.' I try to fight that. That's why I have a clock on my wall that runs counter-clockwise."

Grace Hopper

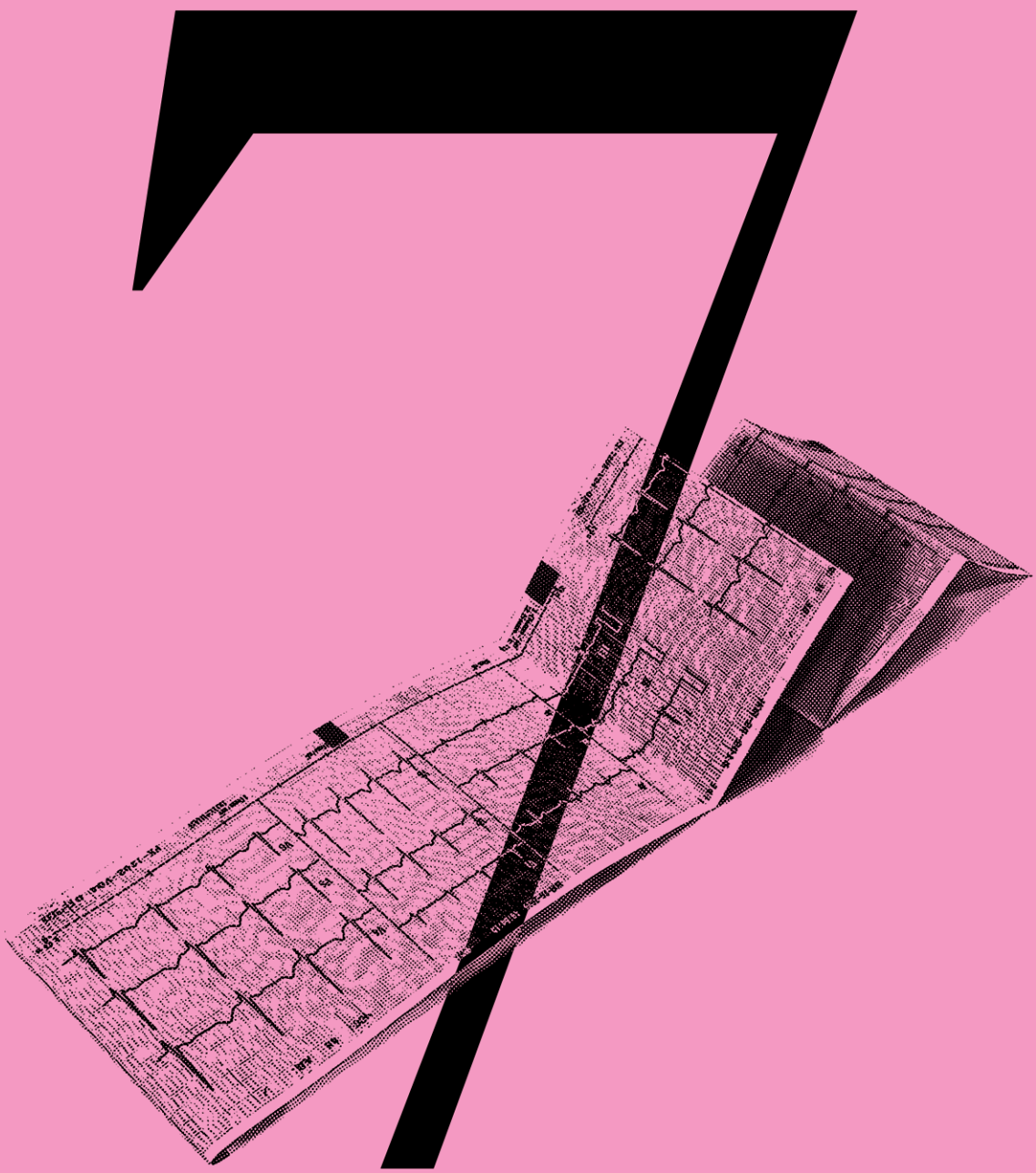
Repeated attempts have been made, and several criteria have been suggested, to distinguish TS from AMI/STEMI according to ECG; none of which can separate the two conditions reliably enough to avoid coronary angiography [14]. While some authors more than others have emphasized ECG differences between TS and AMI [60, 117], the ECG similarities between the two conditions have been recurrently demonstrated [22, 118, 120, 169]. As covered above, attempting to identify ECG differences to separate TS from AMI/STEMI may therefore not be feasible, perhaps because of common elements in the pathophysiology of both conditions. Although not optimal as a diagnostic tool to separate TS from STEMI, ECG may provide valuable information for risk stratification purposes, as well as for as reflecting the phase of TS or providing clues regarding pathophysiology.

Regarding the pathophysiology of TS, the direct catecholamine toxicity theory has gained most attention over the last years [172]. In short, the basis of the direct catecholamine theory includes the apico-basal distribution of beta-adrenergic receptors in studied mammalian animals, parallels to other conditions with excess of catecholamines [5, 172], animal studies of TS [173-175] and detailed theoretical reasoning regarding the effects of catecholamines on the cardiomyocyte on the cellular and subcellular level [5, 172]. Unlike the direct catecholamine toxicity theory, the theory of microvascular dysfunction in TS is based on the pathophysiology of coronary blood circulation in response to sympathetic stimulation [36], and on observations of microvascular disturbances in human subjects with TS [17, 33-35, 37]. Based primarily on the findings of microcirculatory disturbances in patients with TS, there may be reason to advance the vascular/ischemic theory further. Future research regarding diagnostic approaches, outcome and pathophysiology of TS may gain from targeting the cardiac microcirculation. Within this area, differences between men and women regarding coronary microvascular and endothelial dysfunction should be elucidated.

The observations in this thesis may be linked to an ischemic/microvascular pathophysiology of TS, but not to the direct catecholamine toxicity theory, mainly because of the lack of studies regarding ECG changes caused by direct catecholamine toxicity on the cardiomyocyte. An important question in this context is if microcirculatory dysfunction is a possible cause of TS, or a consequence of direct catecholamine toxicity. However, the evidence of microvascular ischemia as a cause of cardiomyocyte damage [33, 50]; and the previously emphasized lack of evidence for microvascular dysfunction/spasm due to catecholamine toxicity [176]; may indicate microvascular dysfunction as a possible cause rather than a consequence. Of note, the microvascular theory is less complicated in comparison to the direct catecholamine toxicity theory, where the former relates broadly through observations to the pathophysiology of cardiac ischemia; perhaps making it the simplest and most applicable theory regarding the pathophysiology of TS.

"With all things being equal, the simplest
explanation tends to be the right one."

William of Ockham



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APPENDICES

Supplementary Table 1. ECG changes from day 0 to 30 for patients with ECG recording within 60 minutes from symptom onset.

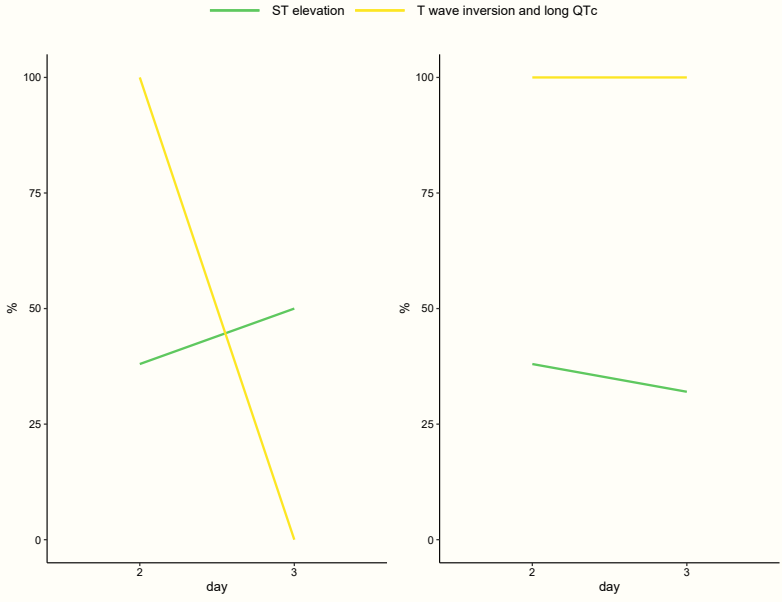
	Model A*	Model B1†
	OR (95% CI)	OR (95% CI)
Takotsubo syndrome versus anterior STEMI, females		
T wave inversion (%)	1.9 (0.58 – 6.4)	1.7 (0.48 – 6.0)
Maximum T wave inversion (mm)	2.6 (0.48 – 14)	2.0 (0.33 – 12)
Average T wave inversion per lead (mm)	1.1 (0.67 – 1.9)	1.1 (0.62 – 1.9)
ST elevation (%)	NA	NA
ST elevation (%) ‡	1.2 (0.46 – 3.5)	1.8 (0.59 – 6.3)
Q wave pathology (%)	0.73 (0.096 – 5.6)	0.48 (0.082 – 2.8)
Long QTc (%)	0.33 (0.039 – 2.8)	0.28 (0.033 – 2.4)
Anterior STEMI, females versus males		
T wave inversion (%)	2.2 (0.62 – 7.9)	2.4 (0.60 – 9.4)
Maximum T wave inversion (mm)	4.0 (1.3 – 12)	4.4 (1.3 – 14)
Average T wave inversion per lead (mm)	1.5 (1.0 – 2.1)	1.5 (0.99 – 2.2)
ST elevation (%)	0.53 (0.068 – 4.2)	0.51 (0.059 – 4.4)
Q wave pathology (%)	0.19 (0.026 – 1.5)	0.16 (0.018 – 1.5)
Long QTc (%)	1.2 (0.23 – 6.5)	1.8 (0.34 – 9.2)

*Univariable, †adjusted for age, hypertension, chronic obstructive pulmonary disease and treatment with beta-blockers, ‡no random effect included; STEMI = ST elevation myocardial infarction, NA = not applicable (few outcome observations after day 3).

Temporal changes in ST elevation and the composite of T wave inversion and long QTc in STEMI and female Takotsubo.

ECG day, diagnosis	0	1	2	7	p 0 vs 1	p 0 vs 2	p 1 vs 7	p 2 vs 7
Anterior STEMI, female								
ST elevation	93% (28/30)	57% (13/23)	46% (12/26)	39% (10/26)	0.0015 ↓	<0.0001 ↓	0.20 →	0.57 →
T inversion + long QTc	10% (3/30)	58% (14/24)	52% (14/27)	15% (4/26)	0.00014 ↑	0.00056 ↑	0.0015 ↓	0.0051 ↓
Anterior STEMI, male								
ST elevation	90% (61/68)	62% (36/58)	48% (25/52)	32% (17/53)	0.00024 ↓	<0.0001 ↓	0.0016 ↓	0.094 →
T inversion + long QTc	14% (10/69)	46% (26/57)	73% (38/52)	20% (11/54)	0.00012 ↑	<0.0001 ↑	0.0048 ↓	<0.0001 ↓
Takotsubo syndrome, female								
ST elevation	62% (18/29)	35% (6/17)	22% (4/18)	14% (3/22)	0.079 →	0.0078 ↓	0.14 →	0.68 →
T inversion + long QTc	17% (5/29)	59% (10/17)	89% (16/18)	41% (9/22)	0.0037 ↑	<0.0001 ↑	0.27 →	0.0018 ↓

The presented days correspond to initial T wave inversion and QT prolongation (day 0 to 1 or 2) as well as pseudo-normalization (day 1 or 2 to 7). STEMI = ST elevation myocardial infarction; QTc = corrected QT interval. Arrows indicate the direction of differences in the ECG variables between the investigated days (↑ = increase, ↓ = decrease, → = no change).



Supplementary Figure 1. Pattern of ST elevation versus T wave inversion and long QTc in patients with and without pseudo-normalization day 2 to 3.

Left: ST elevation versus T wave inversion and long QTc among patients with TS or STEMI who had pseudo-normalized from day 2 to 3 (69 day 2, 52 day 3).

Right: ST elevation versus T wave inversion and long QTc among patients with TS or STEMI with persistent T wave inversion and QT prolongation from day 2 to 3 (69 day 2, 44 day 3). QTc = corrected QT interval, TS = Takotsubo syndrome, STEMI = ST elevation myocardial infarction.