Temporal and Mechanistic Insights into Stress-Induced and Ischemic Cardiomyopathy

Stunning in Takotsubo versus Acute Myocardial Infarction - The STAMI study

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Gothenburg 2026

Cover illustration: **Josefin Bengtsson**

Hand-rendered in graphite in the tradition of classical medical engravings, the illustration portrays the heart in its passage from injury through stunning to recovery — a quiet reflection on vulnerability, time, and the enduring resilience to heal.

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ISBN 978-91-8115-711-6 (PRINT)
ISBN 978-91-8115-712-3 (PDF)

Printed in Borås, Sweden 2026
Printed by Stema Specialtryck AB

Even if you are not ready for the day, it cannot always be night

ABSTRACT

Background: Myocardial stunning is characterized by transient but prolonged left ventricular (LV) dysfunction that persists despite restoration of coronary perfusion. It represents a key pathophysiological feature of two clinically overlapping yet mechanistically distinct conditions: ST-elevation myocardial infarction (STEMI) and Takotsubo syndrome (TS). While STEMI is caused by acute coronary occlusion and ischemic injury, TS is a stress-induced cardiomyopathy occurring in the absence of obstructive coronary disease. Despite similarities in presentation, differences in recovery patterns, myocardial mechanics, inflammatory activation, and complication profiles remain incompletely understood.

Methods: The Stunning in Takotsubo versus Acute Myocardial Infarction (STAMI) study enrolled patients with STEMI or TS on a prospective basis. Standardized serial echocardiography was performed at admission and on days 1, 2, 3, 7, 14, and 30. Additional assessments included electrocardiography, biomarker sampling, biobanking, and cardiac magnetic resonance imaging in a subset of participants.

Six sub-studies evaluated quantitative indices of myocardial dysfunction, myocardial strain, left ventricular (LV) thrombus formation, and plasma proteomic profiles.

Results: Study I – Quantitative Assessment of Myocardial Dysfunction: Continuous indices of regional wall motion abnormality; proportion akinesia (PrA), and proportion akinesia/hypokinesia (PrAH), were validated, demonstrating low inter- and intra-observer variability.

Study II – Temporal Recovery in Women with TS and Anterior STEMI: Despite marked initial impairment, both TS and anterior STEMI were associated with substantial improvement in regional myocardial function beyond day 7, as assessed by PrA. No significant differences were observed in the overall recovery time course between the two conditions.

Study III – Sex Differences in Ischemic Recovery: Among patients with anterior STEMI, women demonstrated greater improvement in PrA and LV ejection fraction (LVEF) at 30 days compared with men.

Study IV – Strain Characteristics and Myocardial Recovery: Global myocardial strain was significantly reduced in both TS and STEMI at presentation. Longitudinal strain was more severely affected in TS, even in

segments away from akinetic regions. No correlation was observed between Global Longitudinal Strain (GLS) and global radial strain (GRS) in TS.

Study V – LV Thrombus Formation: LV thrombus formation was observed exclusively in patients with STEMI, predominantly in anterior infarctions, and not in patients with TS. The occurrence of thrombus was associated with reduced LVEF and higher troponin concentrations.

Study VI – Plasma Proteomic Signatures: Distinct plasma proteomic profiles differentiated STEMI from TS. STEMI was characterized by activation of complement pathways, acute-phase inflammatory signaling, and alterations in lipid metabolism, whereas TS demonstrated a more regulated stress-response profile.

Conclusion: Across the STAMI study, myocardial stunning was identified as a shared and quantifiable feature of both TS and STEMI. Despite similar early recovery dynamics, overall resolution was more complete in TS, and recovery was greater in women than in men after anterior STEMI. Reduced global and segmental strain in the acute phase, with subsequent improvement, reflects reversible myocardial dysfunction, while LV thrombus occurred exclusively in STEMI. Distinct proteomic profiles further differentiated the conditions and identified candidate pathways for future exploration.

Keywords: Myocardial stunning, ST-elevation myocardial infarction, Takotsubo syndrome, Echocardiography

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: När hjärtats pumpförmåga plötsligt försämras kan orsakerna vara olika, även om symtomen ofta är likartade. ST-höjningsinfarkt (STEMI) och Takotsubo-syndrom (TS) är två tillstånd som kan ge bröstsmärta, EKG-förändringar och tydligt nedsatt hjärtfunktion. Trots dessa kliniska likheter skiljer sig de bakomliggande sjukdomsprocesserna.

Vid STEMI täpps ett kranskärl till av en blodpropp, vilket leder till akut syrebrist och risk för bestående skada på hjärtmuskeln. TS utlöses däremot ofta av kraftig emotionell eller fysisk stress och innebär en övergående påverkan på hjärtmuskeln utan att något kranskärl är blockerat. Denna tillfälliga funktionsnedsättning, kallad myokardiell stunning, innebär att hjärtmuskeln är kraftigt försvagad men samtidigt har förmåga att återhämta sig. För att förbättra diagnostik, uppföljning och behandling behövs ökad kunskap om hur återhämtningen ser ut över tid och vilka faktorer som påverkar risken för komplikationer.

Metod: I STAMI-studien (Stunning in Takotsubo versus Acute Myocardial Infarction) följdes patienter med STEMI eller TS under den första månaden efter insjuknandet. Hjärtfunktionen bedömdes med upprepade ultraljudsundersökningar enligt ett standardiserat protokoll och blodprover togs vid flera tillfällen för att analysera inflammatoriska och andra biologiska processer. Genom att kombinera bilddiagnostik och laboratorieanalyser skapades en mer heltäckande bild av hur hjärtat påverkas och återhämtar sig vid dessa två tillstånd.

Delarbete I – Att mäta hjärtmuskelns rörelse på ett nytt sätt: Två nya metoder utvecklades för att mer exakt kunna mäta hur stor del av hjärtmuskeln som rör sig sämre än normalt. Metoderna visade god överensstämmelse mellan olika bedömare och gjorde det möjligt att följa förändringar i hjärtfunktionen över tid på ett mer objektivt och tillförlitligt sätt.

Delarbete II – Hur hjärtat återhämtar sig efter TS och hjärtinfarkt: Kvinnor med TS eller främre STEMI hade initialt kraftigt nedsatt hjärtfunktion. Under de första veckorna sågs dock en tydlig och successiv förbättring, ofta med fortsatt återhämtning efter den första veckan. Några tydliga skillnader i hur snabbt hjärtat återhämtade sig mellan tillstånden kunde inte påvisas.

Delarbete III – Skillnader mellan kvinnor och män vid hjärtinfarkt: Kvinnor med främre hjärtinfarkt förbättrade sin hjärtfunktion mer under den första månaden jämfört med män, vilket tyder på möjliga biologiska skillnader i hur hjärtat återhämtar sig efter syrebrist.

Delarbete IV – Förändringar i hjärtats töjningsförmåga (strain): Global strain var tydligt nedsatt vid insjuknandet i TS och STEMI. Longitudinell strain föreföll dock vara mer uttalat påverkad vid TS, även i områden utanför de mest nedsatta segmenten. Avsaknad av korrelation mellan longitudinell och radiell strain vid TS talar för en mer selektiv påverkan på olika lager av myokardiet, medan påverkan vid STEMI föreföll vara mer genomgående.

Delarbete V – Blodpropp i hjärtat: Blodpropp i vänster hjärtkammare sågs endast hos patienter med STEMI, men inte hos patienter med TS. Risken var tydligt kopplad till hur mycket hjärtats pumpförmåga var nedsatt under det akuta skedet.

Delarbete VI – Analys av proteiner i blodet: Analyser av blodprover visade tydliga biologiska skillnader mellan tillstånden. Vid STEMI noterades en kraftigare aktivering av inflammations- och komplementsystemet, medan TS präglades av en mer reglerad stress- och inflammationsrespons. Dessa biologiska mönster speglade också skillnader i återhämtningsförlopp.

Slutsats: Avhandlingen visar att myokardiell stunning är ett centralt fenomen vid både STEMI och TS och att hjärtats funktion ofta återhämtar sig successivt under den första månaden. Samtidigt finns viktiga skillnader i bakomliggande mekanismer och risk för komplikationer. Genom att kombinera upprepade hjärtundersökningar med molekylära analyser kan förståelsen för reversibel hjärtmuskelskada förbättras och bidra till en mer individanpassad behandling vid akut hjärtsjukdom.

Nyckelord: Ekokardiografi, myokardiell stunning, Takotsubosyndrom, ST-höjningsinfarkt, könsskillnader, Blodpropp

LIST OF PAPERS

This thesis is based on six papers, hereafter referred to in the text by Roman numerals.

I. Poller A, Jha S, et al. *Inter- and intra-observer variability in the echocardiographic evaluation of wall motion abnormality in patients with ST-elevation myocardial infarction or Takotsubo syndrome – a novel approach.* Echocardiography. 2023;40:711–719

II. Jha S, Poller A, et al. *Prospective comparison of temporal changes in myocardial function in women with Takotsubo syndrome versus anterior ST-elevation myocardial infarction.* Clinical Research in Cardiology. 2025;114:1705–1717.

III. Jha S, Shekka Espinosa A, et al. *Prospective comparison of temporal myocardial function in men versus women after anterior ST-elevation myocardial infarction with timely reperfusion.* The American Journal of Cardiology. 2025;244:48–57

IV. Poller A, Jha S, et al. *Global and segmental longitudinal and radial strain in Takotsubo syndrome versus ST-elevation myocardial infarction.* International Journal of Cardiology. 2025;439:133668.

V. Jha S, Poller A, et al. *Left ventricular thrombus in Takotsubo syndrome and ST-elevation myocardial infarction.* Manuscript accepted for publication.

VI. Hussain S, Jha S, et al. *Comparative analysis of plasma protein dynamics in women with ST-elevation myocardial infarction and Takotsubo syndrome.* Cells. 2024;13:1764.

CONTENTS

ABBREVIATIONS

eCRF	Electronic case report form
GLS	Global longitudinal strain
GRS	Global radial strain
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro–B-type natriuretic peptide
PrA	Proportion of akinesia
RV	Right ventricular
STAMI	Stunning in Takotsubo versus Acute Myocardial Infarction
STAMI-BAS	Stunning in Acute Myocardial Infarction – Beta blockers, Angiotensin converting enzyme inhibitors, and Sodium/glucose cotransporter 2 inhibitors trial
STEMI	ST-elevation myocardial infarction
TAPSE	Tricuspid annular plane systolic excursion
TIMI	Thrombolysis in myocardial infarction
TS	Takotsubo syndrome
WMSI	Wall motion score index

INTRODUCTION

MYOCARDIAL STUNNING

Acute myocardial infarction continues to impose a substantial global burden, even in the era of modern cardiovascular care. Advances in early reperfusion strategies have markedly improved survival by rapidly restoring coronary blood flow and limiting irreversible myocardial injury (1-3).

However, restoration of perfusion does not translate into immediate normalization of ventricular function. Many patients demonstrate significant systolic impairment in the early phase despite successful reperfusion. Importantly, this early dysfunction does not necessarily indicate permanent myocardial damage. A considerable proportion of the affected myocardium remains viable but exhibits transient contractile impairment.

This reversible form of myocardial dysfunction is termed ***myocardial stunning*** and represents an important determinant of early ventricular performance after acute cardiac injury (4).

HISTORICAL BACKGROUND

The concept of myocardial stunning emerged from experimental studies of ischemia–reperfusion injury in the late twentieth century (4, 5). These investigations demonstrated that timely restoration of coronary blood flow could preserve myocardial viability despite persistent contractile dysfunction, thereby challenging the earlier assumption that prolonged dysfunction necessarily reflected irreversible necrosis.

Soon thereafter, Heyndrickx and colleagues (6) demonstrated that myocardial contractile function may remain depressed for prolonged periods despite complete restoration of coronary blood flow. Braunwald and Kloner subsequently introduced the term myocardial stunning to describe this delayed recovery of myocardial function in the absence of irreversible myocardial injury (7). These discoveries fundamentally changed the understanding of ischemic heart disease by demonstrating that myocardial viability and mechanical function are not always synonymous (7-9).

PHYSIOLOGY OF MYOCARDIAL STUNNING

A hallmark of myocardial stunning is the dissociation between myocardial perfusion and mechanical function after reperfusion (4). Under normal physiological conditions, myocardial blood flow and contractile performance are tightly coupled through metabolic and mechanical regulatory mechanisms **Figure 1**.

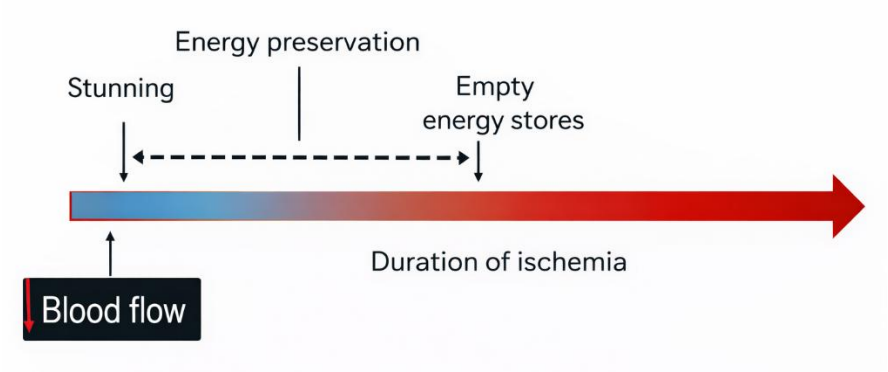


Figure 1: Schematic illustration of transient myocardial dysfunction despite restored perfusion and preserved cellular viability, with gradual recovery of contractile function over time. Created with BioRender.com.

In stunned myocardium, this relationship becomes disrupted. Following reperfusion, coronary blood flow returns to normal or near-normal levels, yet regional contractile dysfunction persists. Importantly, this phenomenon cannot be explained by persistent ischemia, as perfusion in stunned regions exceeds the metabolic threshold required to sustain oxidative metabolism. Reperfusion instead triggers transient intracellular disturbances that impair contractile function despite preserved myocardial viability. These disturbances include oxidative stress, calcium handling abnormalities, mitochondrial dysfunction, and impaired excitation–contraction coupling. As these cellular processes gradually normalize, myocardial contractility typically recovers (10)

CELLULAR MECHANISMS

Multiple cellular mechanisms contribute to the development of myocardial stunning. Experimental studies have identified oxidative stress, disturbances in intracellular calcium regulation, mitochondrial dysfunction, and impaired excitation–contraction coupling as central contributors. During reperfusion, the sudden reintroduction of oxygen can trigger the generation of reactive

oxygen species that can damage cellular proteins and disrupt intracellular signaling pathways. At the same time, alterations in calcium homeostasis can result in intracellular calcium overload, impairing the interaction between calcium and the contractile myofilaments (5, 10).

Mitochondrial dysfunction further contributes to impaired cellular energetics and increased oxidative stress **Figure 2**. Together, these mechanisms impair cardiomyocytes' ability to translate restored perfusion into effective mechanical contraction. Importantly, because cardiomyocytes remain structurally viable, myocardial function gradually recovers as these disturbances resolve (11).

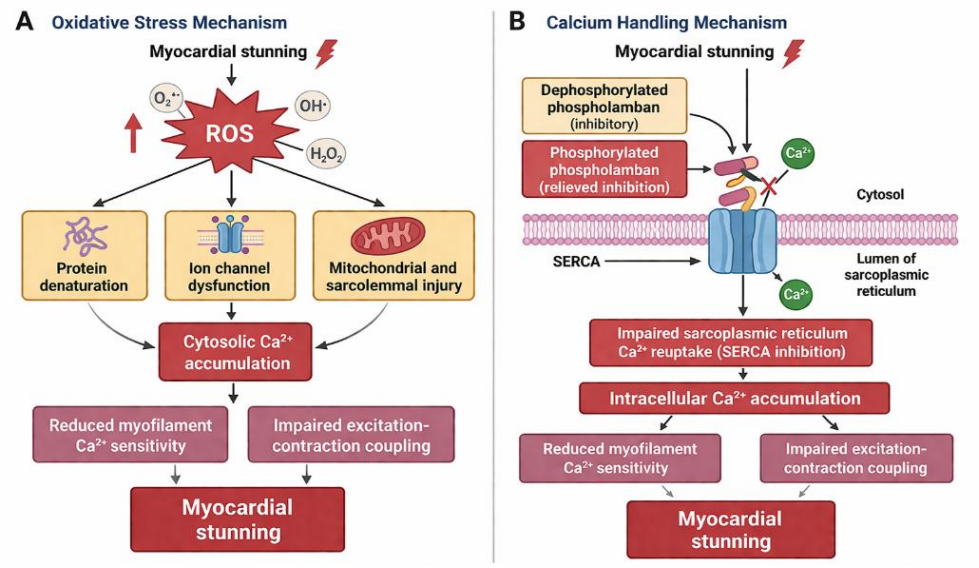


Figure 2: Proposed mechanisms underlying myocardial stunning. (**A**) The oxyradical hypothesis attributes transient contractile dysfunction to oxidative stress generated during early reperfusion. (**B**) The calcium overload hypothesis implicates disturbed intracellular calcium handling and activation of calcium-dependent proteases as key contributors to reversible contractile impairment. Reproduced and recreated with permission from Espinosa A. *Translational studies to understand myocardial stunning in acute myocardial infarction*. ISBN 978-91-8115-006-3 (PDF). Available at: https://hdl.handle.net/2077/84037

IMAGING OF MYOCARDIAL STUNNING

Modern cardiovascular imaging plays a central role in the clinical assessment of myocardial stunning by enabling detailed evaluation of ventricular function, myocardial contractility, valvular function, and tissue characteristics over time (12, 13).

Transthoracic echocardiography is the most widely used imaging modality for evaluating myocardial dysfunction in clinical practice. It allows rapid, noninvasive assessment of global and regional ventricular function and can be repeated serially during the acute and subacute phases of cardiac injury (14, 15). Conventional echocardiographic measures such as left ventricular (LV) ejection fraction and wall motion score index have long been used to quantify myocardial dysfunction following myocardial injury. However, these measures may have limited sensitivity for detecting subtle regional abnormalities or for characterizing the temporal dynamics of myocardial recovery (14-16).

Speckle-tracking echocardiography has expanded the ability to quantify myocardial mechanics through the measurement of myocardial strain. Global longitudinal strain has emerged as a particularly sensitive marker of myocardial dysfunction. Because longitudinal myocardial fibers located in the subendocardium are especially vulnerable to ischemia, global longitudinal strain often detects myocardial injury earlier and more accurately than conventional measures such as ejection fraction (17-19).

Cardiac magnetic resonance imaging provides complementary information by enabling detailed characterization of myocardial tissue properties. Late gadolinium enhancement allows identification of irreversible myocardial injury and infarct size, while T2-weighted imaging can detect myocardial edema associated with acute ischemic injury. In the context of myocardial stunning, cardiac magnetic resonance imaging therefore helps distinguish viable but dysfunctional myocardium from necrotic tissue (20-24).

Together, these imaging modalities enable comprehensive characterization of myocardial dysfunction by integrating functional and structural information. Serial imaging provides unique insight into the temporal evolution of myocardial injury and recovery following acute cardiac events.

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction represents one of the most severe manifestations of ischemic heart disease and remains a leading cause of morbidity and mortality worldwide. It occurs when coronary blood flow becomes critically reduced or interrupted, resulting in ischemic injury to the myocardium. In most cases, this process is triggered by rupture or erosion of an atherosclerotic plaque within a coronary artery, leading to platelet activation, thrombus formation, and obstruction of the vessel lumen **Figure 3**.

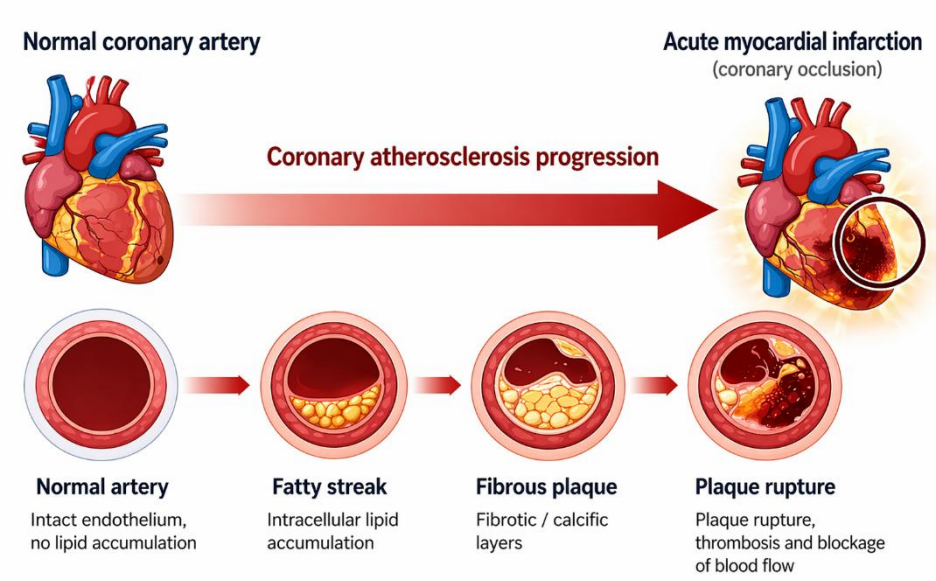


Figure 3: Coronary artery occlusion and subsequent reperfusion resulting in a combination of irreversible myocardial necrosis and surrounding viable but stunned myocardium. Created with BioRender.com.

Clinically, acute myocardial infarction is classified into ST-elevation myocardial infarction (STEMI) and non–STEMI based on electrocardiographic findings and the extent of myocardial ischemia. STEMI represents the most acute form of myocardial infarction and typically results from sudden and complete occlusion of a major epicardial coronary artery. The anatomical location and clinical consequences of STEMI depend largely on the coronary artery involved (1, 3, 25, 26). Occlusion of the left anterior descending artery typically produces anterior myocardial infarction affecting the anterior wall, interventricular septum, and frequently the apex of the left ventricle. Because the left anterior descending artery supplies a substantial

portion of the LV myocardium, anterior infarctions are often associated with more extensive myocardial dysfunction and a higher risk of complications. In contrast, occlusion of the right coronary artery or left circumflex artery generally results in non-anterior infarctions involving the inferior or lateral myocardial walls. These infarctions typically affect smaller myocardial territories and are therefore often associated with less severe global myocardial dysfunction.

The introduction of primary percutaneous coronary intervention has substantially improved survival in patients with STEMI by enabling rapid restoration of coronary blood flow (3, 27). Nevertheless, ventricular function measured early after reperfusion may not fully reflect the ultimate degree of myocardial recovery. Serial imaging studies have demonstrated that ventricular function frequently evolves over the days and weeks following infarction, reflecting the dynamic nature of myocardial injury and recovery (28).

Understanding the determinants of myocardial dysfunction and recovery after acute myocardial infarction is therefore essential for interpreting early imaging findings, assessing prognosis, and identifying patients at risk for complications such as heart failure or LV thrombus formation.

TAKOTSUBO SYNDROME

Takotsubo Syndrome (TS), also known as stress-induced cardiomyopathy or broken heart syndrome, is an acute cardiac condition characterized by transient LV systolic dysfunction occurring in the absence of culprit obstructive coronary artery disease (29, 30). Patients typically present with symptoms and electrocardiographic changes that closely resemble those of acute myocardial infarction, including chest pain, ST-segment elevation, and elevation of cardiac biomarkers. Consequently, the syndrome is often indistinguishable from acute coronary syndromes at initial presentation (31).

The syndrome was first described in Japan in the early 1990s and derives its name from the Japanese word *tako-tsubo*, which refers to a traditional octopus trap whose shape resembles the characteristic left ventricular appearance in affected patients (31, 32) **Figure 4**. Since its initial description, TS has been increasingly recognized worldwide and is estimated to account for approximately 1–3 percent of patients presenting with suspected acute coronary syndrome. TS predominantly affects postmenopausal women, who represent more than 85–90 percent of affected individuals (30, 33-35). In many cases, symptom onset is preceded by an identifiable emotional or physical stressor. This observation has led to the hypothesis that excessive catecholamine release and neurohumoral activation play a central role in the pathophysiology of the syndrome (36).

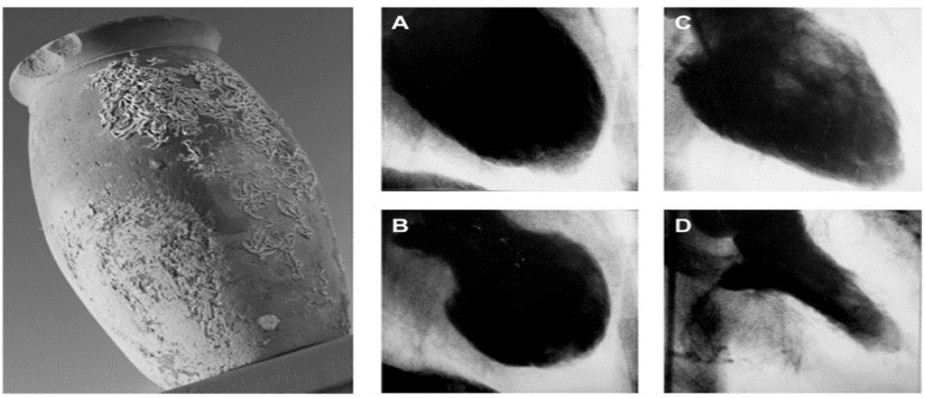


Figure 4: Historical Japanese octopus trap (left). Courtesy of Dr. Templin, University Hospital Zurich, Zurich, Switzerland. Left ventriculogram of the first reported case of TS. Diastole (**A**) and systole (**B**) during the acute phase of TS. Recovery of LV wall motion abnormality two weeks after the event (**C** and **D**). Courtesy of Dr. Dote, Hiroshima City Asa Hospital, Hiroshima, Japan

Cardiac imaging typically demonstrates extensive regional wall motion abnormalities extending beyond a single coronary territory, most commonly involving akinesia of the apical and midventricular segments with preserved or hyperdynamic basal contraction, although variant patterns exist (37, 38).

In this thesis, TS is defined according to the European Society of Cardiology criteria as follows:

- *Transient regional wall motion abnormality.*
- *Wall motion regionality beyond single vascular distributions.*
- *Absence of culprit atherosclerotic coronary artery disease.*
- *New and reversible electrocardiographic abnormalities.*
- *Significantly increased NT-proBNP levels in the acute phase.*
- *Increase in cardiac troponin levels.*
- *Recovery of left ventricular systolic function on cardiac imaging follow-up.*

One notable feature of TS is the apparent dissociation between the severity of acute myocardial dysfunction and the often relatively preserved hemodynamic status (39). Despite marked systolic impairment, ventricular function typically improves rapidly and normalizes within weeks to months.

Despite increasing recognition, evidence-based treatment strategies remain limited. Management is largely supportive and extrapolated from heart failure and acute coronary syndrome therapies, as robust randomized clinical trials are lacking (39, 40).

MYOCARDIAL STUNNING IN CLINICAL SYNDROMES

As previously described, myocardial stunning was first identified in experimental models of ischemia–reperfusion injury but is now recognized as a key mechanism underlying transient myocardial dysfunction across a range of clinical conditions (11). These include reperfused myocardial infarction, cardiac arrest, cardiac surgery, acute myocarditis, and stress-induced cardiomyopathy. In such settings, impaired myocardial contractility may persist despite restoration of coronary blood flow—or even in the absence of overt structural damage—reflecting a temporary dissociation between myocardial viability and mechanical function (9).

Among these clinical scenarios, TS and STEMI represent two particularly informative and complementary human conditions for studying myocardial stunning. Both conditions may present with acute chest pain, electrocardiographic abnormalities, elevated cardiac biomarkers, and regional wall motion abnormalities detectable on cardiac imaging (41, 42). Despite these similarities in early clinical presentation, the underlying mechanisms of myocardial dysfunction, the balance between reversible and irreversible injury, and the patterns of recovery differ substantially (39, 43).

In STEMI, myocardial stunning develops primarily as a consequence of acute coronary occlusion followed by reperfusion. Restoration of blood flow limits infarct size but initiates a cascade of reperfusion-related processes, including calcium overload, oxidative stress, mitochondrial dysfunction, and transient impairment of excitation–contraction coupling. As a result, myocardial dysfunction in the acute phase reflects a combination of irreversible myocardial necrosis within the infarct core and reversible contractile dysfunction in surrounding viable myocardium. This stunned myocardium contributes significantly to early systolic impairment and the development of acute ischemic heart failure, even in patients with successful reperfusion therapy. Importantly, the extent of myocardial recovery over time depends not only on infarct size but also on the magnitude and duration of myocardial stunning (44).

In contrast, myocardial stunning in TS occurs in the absence of an acute epicardial coronary occlusion and is instead likely mediated by a sudden surge in catecholamines and intense sympathetic activation. Excessive adrenergic

stimulation alters β-adrenergic receptor signaling in cardiomyocytes, leading to negative inotropic effects and acute contractile dysfunction. In addition, catecholamine excess may promote coronary microvascular dysfunction, vasospasm, metabolic mismatch, intracellular calcium dysregulation, and myocardial energy depletion. These mechanisms result in extensive but typically reversible regional myocardial dysfunction, often extending beyond the territory of a single coronary artery (44).

Despite the profound systolic impairment observed in the acute phase of TS, structural myocardial injury is usually limited, with minimal fibrosis or permanent scar formation. Myocardial contractility therefore recovers in most patients over days to weeks (35, 45). From a pathophysiological perspective, TS may represent a more diffuse and advanced form of myocardial stunning, in which neurohumoral stress, rather than ischemic necrosis, predominates as the principal driver of myocardial dysfunction **Figure 5**. Consequently, STEMI and TS together provide complementary clinical frameworks for understanding how myocardial stunning interacts with myocardial injury, ventricular remodeling, and clinical outcomes in acute cardiac disease.

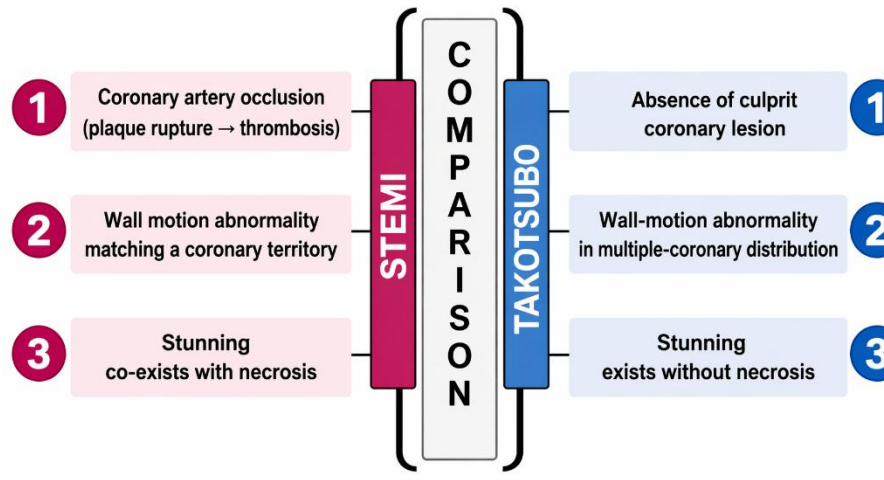


Figure 5: Conceptual illustration of comparison of myocardial stunning in STEMI and TS. Created with BioRender.com.

Comparative investigation of these syndromes offers a unique opportunity to elucidate the temporal evolution, mechanistic pathways, and prognostic implications of myocardial stunning in the human heart.

SEX DIFFERENCES IN MYOCARDIAL RECOVERY

Cardiovascular disease exhibits pronounced sex-related differences in incidence, presentation, and outcomes (46). TS predominantly affects postmenopausal women, whereas STEMI has historically been more common in men (47-49). Experimental and clinical data suggest that hormonal regulation, inflammatory responses, and myocardial remodeling processes may differ between sexes. Emerging data further suggest that myocardial stunning may contribute differently to early clinical manifestations across patient subgroups.

Women appear more likely than men to develop acute ischemic heart failure after STEMI despite a similar infarct size (50, 51), raising the possibility that stunned but viable myocardium plays a more prominent role in the development of acute myocardial dysfunction in women. Interestingly, this increased susceptibility to heart failure does not consistently translate into higher mortality, suggesting a complex interaction between sex-specific myocardial responses to ischemia, contractile reserve, neurohumoral activation, and subsequent recovery (46).

Understanding whether recovery kinetics and susceptibility to complications vary by sex is essential for individualized risk stratification and management. However, prospective studies with systematic temporal imaging and quantitative functional assessment have been limited.

THROMBOTIC COMPLICATIONS AND FUNCTIONAL SEVERITY

The degree of LV dysfunction following acute myocardial injury is closely linked to thrombotic risk. In patients with STEMI, extensive regional akinesia may promote blood stasis within the ventricular cavity, contributing to thrombus formation (52-54). LV thrombus formation carries a significant risk of systemic embolization, including ischemic stroke and peripheral embolic events. Identifying patients at risk, therefore, remains an important clinical challenge (52).

TS mimics STEMI and often presents with extensive regional akinesia and marked systolic dysfunction, potentially creating a substrate for thrombus formation. However, the absence of transmural myocardial necrosis and the typically transient nature of myocardial dysfunction may attenuate the overall

thrombogenic potential, and the true thrombotic risk in these patients remains incompletely understood (55, 56).

Clarifying the relationship between myocardial dysfunction and thrombotic risk requires systematic imaging and prospective evaluation across different forms of acute cardiomyopathy.

INTEGRATIVE PHENOTYPING IN ACUTE CARDIOMYOPATHY

Contemporary cardiovascular research increasingly emphasizes integrative phenotyping, linking detailed imaging characterization with molecular profiling and longitudinal clinical outcomes. This approach enables a more comprehensive understanding of disease mechanisms beyond traditional clinical descriptors.

Serial echocardiography allows quantification of regional myocardial dysfunction and tracking of myocardial recovery over time. Strain imaging further enhances this capability by enabling sensitive detection of subtle myocardial mechanical abnormalities that may not be apparent using conventional measures such as ejection fraction. In parallel, advances in proteomic technologies have enabled large-scale characterization of circulating proteins involved in inflammatory signaling, metabolic regulation, and cellular stress responses during acute cardiac injury. Plasma proteomic profiling, therefore, provides a unique window into the molecular processes accompanying myocardial injury and recovery.

KNOWLEDGE GAPS

Despite extensive research on myocardial injury and recovery, important questions remain regarding the mechanisms and temporal evolution of myocardial dysfunction following acute cardiac events. Myocardial stunning is recognized as a major contributor to transient myocardial dysfunction, yet several key aspects remain incompletely understood.

Key unresolved questions include:

Expression of myocardial stunning
It remains unclear whether myocardial stunning is expressed similarly in TS and STEMI. Although both conditions present with acute myocardial dysfunction, the extent and distribution of affected myocardium may differ.

Time course of recovery
Whether recovery from myocardial stunning follows similar or distinct trajectories in TS and STEMI remains unclear.

Sex differences in myocardial recovery
The influence of biological sex on the extent and pattern of myocardial recovery remains uncertain, particularly given the predominance of TS among women.

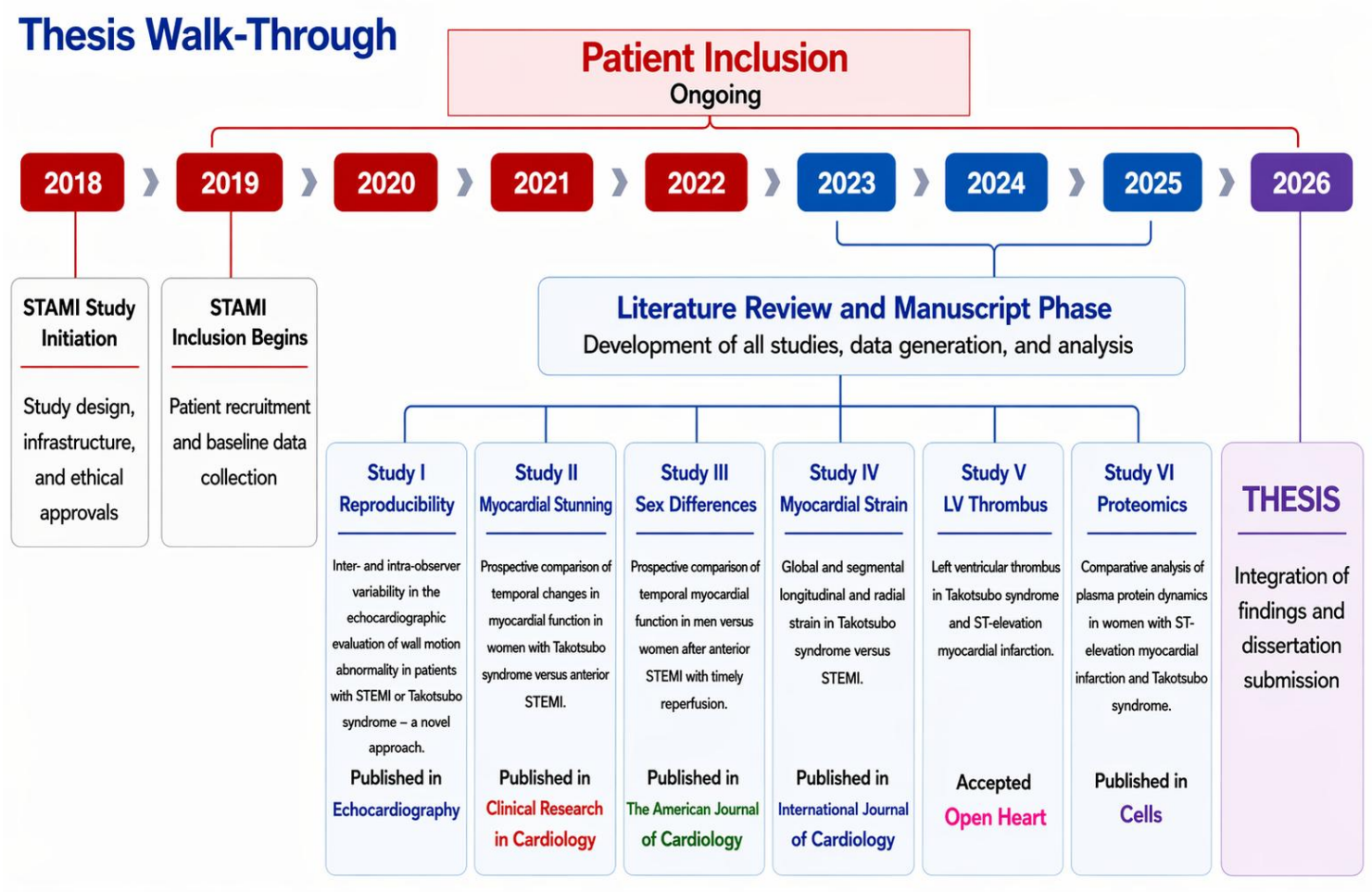
Stunning-related complications
It is unclear whether complications associated with severe myocardial dysfunction, such as LV thrombus formation, occur with similar frequency across these conditions.

Molecular determinants of myocardial injury and recovery
While cardiac imaging provides a detailed assessment of ventricular function, the molecular pathways underlying myocardial injury and recovery are less well defined. Proteomic approaches may help identify circulating signatures of myocardial dysfunction and improve differentiation between ischemic and stress-induced cardiomyopathy.

Addressing these gaps requires integrative strategies combining longitudinal imaging, molecular profiling, and detailed clinical phenotyping.

THE STAMI RESEARCH PROGRAM

The **Stunning Takotsubo versus Acute Myocardial Infarction** (STAMI) research program was initiated to address key knowledge gaps and provide a comprehensive characterization of myocardial stunning in TS and STEMI. By combining serial echocardiography, quantitative functional assessment, strain imaging, proteomic profiling, and structured follow-up, STAMI enables a detailed evaluation of both the evolution and underlying mechanisms of myocardial dysfunction.


Thesis Walk-Through
Patient Inclusion
Ongoing
2018
2019
2020
2021
2022
2023
2024
2025
2026
STAMI Study Initiation
Study design, infrastructure, and ethical approvals
STAMI Inclusion Begins
Patient recruitment and baseline data collection
Literature Review and Manuscript Phase
Development of all studies, data generation, and analysis
Study I
Reproducibility
Inter- and intra-observer variability in the echocardiographic evaluation of wall motion abnormality in patients with STEMI or Takotsubo syndrome – a novel approach.
Published in
Echocardiography
Study II
Myocardial Stunning
Prospective comparison of temporal changes in myocardial function in women with Takotsubo syndrome versus anterior STEMI.
Published in
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Study III
Sex Differences
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LV Thrombus
Left ventricular thrombus in Takotsubo syndrome and ST-elevation myocardial infarction.
Accepted
Open Heart
Study VI
Proteomics
Comparative analysis of plasma protein dynamics in women with ST-elevation myocardial infarction and Takotsubo syndrome.
Published in
Cells
THESIS
Integration of findings and dissertation submission

Figure 6: Thesis Walk-Through.
Overview of the STAMI study and thesis timeline, illustrating ongoing patient enrollment, the literature review and manuscript phase, and the sequential development of six interrelated studies culminating in the doctoral thesis.

AIM

The overall aim of this thesis was to deepen the understanding of myocardial stunning by investigating the temporal evolution, biological determinants, and clinical consequences of reversible myocardial dysfunction in both TS and STEMI. By integrating longitudinal cardiac imaging, detailed clinical phenotyping, and molecular profiling, this work sought to characterize patterns of myocardial recovery, identify modifiers of recovery dynamics, and explore complications associated with severe myocardial dysfunction.

To address this aim, the following specific objectives were investigated:

Study I: To develop and validate reproducible quantitative indices of regional myocardial wall motion abnormality in patients with TS and STEMI, and to evaluate their inter- and intra-observer variability.

Study II: To prospectively characterize the temporal evolution of myocardial recovery in women with TS and anterior STEMI using serial echocardiography.

Study III: To investigate sex-related differences in the magnitude and trajectory of myocardial recovery following anterior STEMI.

Study IV: To compare global and regional myocardial strain parameters in acute TS and STEMI and to evaluate longitudinal recovery patterns using speckle-tracking echocardiography.

Study V: To prospectively evaluate the incidence, timing, and determinants of LV thrombus formation in patients with TS and STEMI.

Study VI: To characterize temporal plasma proteomic profiles in patients with STEMI and TS and to identify molecular pathways associated with reversible versus irreversible myocardial injury.

PATIENTS AND METHODS

GENERAL STUDY DESIGN

The Stunning in Takotsubo versus Acute Myocardial Infarction (STAMI, NCT04448639) is an ongoing prospective observational study conducted at the Department of Cardiology, Sahlgrenska University Hospital in Gothenburg, Sweden.

Although the study is conducted at a single tertiary care center, Sahlgrenska University Hospital is the primary referral center for patients with acute cardiac conditions in Region Västra Götaland. Patients presenting with suspected STEMI or TS from across the region are routinely referred to Sahlgrenska University Hospital for urgent coronary angiography and specialized cardiology care. Consequently, patients admitted to Sahlgrenska University Hospital with these conditions were eligible for screening and potential inclusion in the study.

Participants were enrolled during their initial hospital stay and monitored following a specific study protocol throughout their hospitalization and during scheduled follow-up visits **Figure 7**.

STUDY COHORTS

Eligible patients presenting with STEMI or TS, both defined as per European Society of Cardiology guidelines, were consecutively screened for inclusion. Patients diagnosed with STEMI were further categorized as having anterior or non-anterior STEMI based on electrocardiographic criteria. Anterior STEMI was defined as ST-segment elevation in two contiguous anterior leads (V1–V4). Non-anterior STEMI was defined as STEMI that did not meet criteria for anterior infarction.

Inclusion Criteria

- Diagnosis of STEMI or TS as per ESC criteria
- Coronary angiography within 12 hours of symptom onset
- Age ≥18 years
- Absence of pre-existing LV wall motion abnormalities

Exclusion Criteria

- Cardiogenic shock at presentation (Killip class IV)
- Expected inability to comply with the study protocol

Additional exclusion criteria for the MRI substudy

- Estimated glomerular filtration rate <30 ml/kg/min
- Claustrophobia or inability to tolerate confined spaces.
- Any other contraindications for MRI as per local guidelines

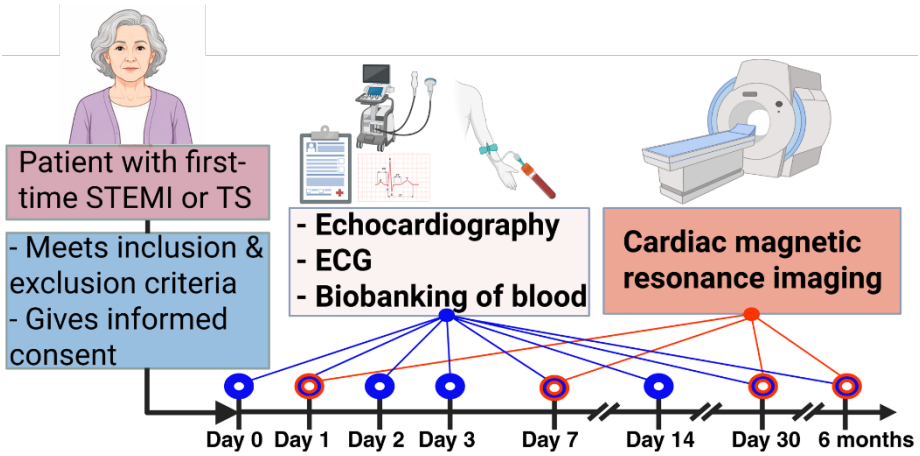


Figure 7: Schematic illustration of the STAMI study. Created with BioRender.com.

STUDY PROCEDURES AND FOLLOW-UP

All participants underwent standardized assessments according to the STAMI study protocol. Clinical data, electrocardiography, cardiac imaging, laboratory parameters, and plasma samples were collected at predefined time points during hospitalization and follow-up. An overview of the study procedures and timing of assessments is presented in **Table 1**.

During the index hospitalization, patients were monitored in accordance with standard clinical practice in the coronary care or cardiology ward. Continuous telemetry monitoring was carried out during the acute phase. Vital signs, including blood pressure and heart rate, were measured regularly, and serial laboratory tests were performed as part of routine care. Serial cardiac imaging was conducted at preset time points during the acute and subacute phases. In a

subset of patients, cardiac magnetic resonance imaging was also performed following the study protocol.

Table 1. Study-related procedures/Schedule of events

Study Procedure	Baseline	24 ± 6 h	48 ± 12 h	72 ± 12 h	7 days ± 24 h	14 days ± 48 h	30 days ± 48 h
Informed consent	•						
Eligibility criteria	•						
History and risk factors	•						
Chest pain questionnaire	•						
Recording of medications	•	•	•	•	•	•	•
Continuous telemetry monitoring*	•	•	•	•			
Blood pressure and heart rate†	•	•	•	•	•	•	•
12-Lead ECG	•	•	•	•	•	•	•
Echocardiography	•	•	•	•	•	•	•
Cardiac MRI$		•			•		•
NT-proBNP and troponins	•	•	•	•	•	•	•
Routine laboratory tests§	•						
Plasma biobanking (proteomics)	•	•	•	•	•	•	•

*Continuously recorded during index hospitalization. †Blood pressure and heart rate measured every 12 hours—§ Including serum creatinine, hemoglobin, white blood cells, and electrolytes. Up to 5 MRIs are performed between day 24 and day 180. ECG = electrocardiography.

DATA MANAGEMENT

All study data were recorded in a dedicated electronic case report form (eCRF) developed for the STAMI study, using a REDCap database hosted by the University of Gothenburg. Each participant was assigned a unique STAMI study identification number at the time of enrollment. Personal identifiers were stored separately from the study database to protect participant confidentiality.

Clinical characteristics, imaging findings, laboratory measurements, and follow-up data were entered into the eCRF by authorized study personnel. Data management and handling were carried out in accordance with local data protection regulations and institutional guidelines at Sahlgrenska University Hospital, as well as the General Data Protection Regulation (EU 2016/679).

STATISTICAL AND METHODOLOGICAL CONSIDERATIONS

Given the longitudinal design of the STAMI study, with repeated imaging, biomarker sampling, and clinical assessments over time, the analytical approach was designed to capture both population-level trends and individual recovery trajectories. Particular emphasis was placed on accounting for within-patient correlations and the dynamic nature of myocardial recovery after acute cardiac injury.

Longitudinal changes in myocardial function were primarily analyzed using mixed-effects regression models. These models allow simultaneous estimation of overall trends while accommodating patient-specific variation, providing a flexible framework for analyzing repeated measurements with incomplete follow-up. This approach was particularly suited to the STAMI dataset, where recovery trajectories varied substantially between individuals and over time.

Regional myocardial dysfunction was quantified using the proportion of akinesia (PrA), a continuous measure derived from echocardiographic assessment. As myocardial function improved over time, PrA values frequently approached zero, resulting in a left-censored distribution. To account for this, tobit mixed-effects models were applied in selected analyses. Time was generally treated as a categorical variable to reflect the predefined follow-up schedule and to avoid assumptions about the shape of recovery trajectories.

To explore clinical determinants of complications, time-to-event analyses were performed using Cox proportional hazards models. In these analyses, echocardiographic and biomarker variables were incorporated as time-varying covariates when appropriate, allowing the models to reflect the evolving physiological state during the acute phase.

Proteomic analyses required a complementary analytical framework due to the data's high dimensionality. Protein expression levels were normalized and log-transformed prior to analysis, and differential expression was evaluated with adjustment for multiple testing using false discovery rate procedures. Subsequent enrichment analyses were performed to identify biological pathways associated with myocardial injury and recovery, linking molecular patterns to clinical and imaging findings.

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate, and categorical variables as frequencies and percentages. Detailed descriptions of study-specific statistical methods are provided in the respective sections below.

STUDY-SPECIFIC METHODS

STUDY I

Population

Patients from the STAMI cohort with adequate baseline echocardiographic image quality to reliably assess regional wall motion abnormalities were included in the analysis.

Methodological Focus

Regional myocardial dysfunction was quantified using continuous indices derived from apical echocardiographic views **Figure 8**.

Proportion Akinesia (PrA) and Proportion Akinesia and Hypokinesia (PrAH) evaluate wall motion abnormalities without the use of pre-defined segments. It allows investigation of LV regional wall motion differences over time when performed repeatedly. PrA is defined as the sum of the total length of akinetic endocardium in end-diastole, measured in apical four- and two-chamber views, divided by the total length of the left ventricle endocardium in end-diastole (measured in apical four- and two-chamber views), multiplied by 100:

$$\boldsymbol{PrA}\ (\%) = \frac{\boldsymbol{Total\ akinetic\ endocardium}}{\boldsymbol{Total\ endocardial\ length}}\boldsymbol{x100}$$

Calculation of PrA and PrAH is illustrated in **Figure 8**. For comparison with conventional echocardiographic assessment, the wall motion score index (WMSI) was also calculated. The left ventricle was divided into 17 segments at basal, midventricular, and apical levels according to standard echocardiographic segmentation. Each segment was visually scored as normal or hyperkinetic (1), hypokinetic (2), akinetic (3), or dyskinetic (4). WMSI was defined as the mean score across all analyzed segments.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation for normally distributed data and as median (interquartile range) for skewed distributions. Categorical variables are reported as counts and percentages.

Inter-observer agreement for the presence or absence of akinesia was assessed using Cohen's kappa coefficient. For quantitative measurements of regional

dysfunction, inter- and intra-observer variability in the proportion of akinesia (PrA) and WMSI were evaluated by calculating mean differences and standard deviations between repeated measurements.

Measurement reliability was assessed using intraclass correlation coefficients (ICC), with values >0.80 considered indicative of excellent agreement. Internal consistency was evaluated using Cronbach's alpha. Agreement between observers was further examined using Bland–Altman plots, which display the difference between measurements against their mean.

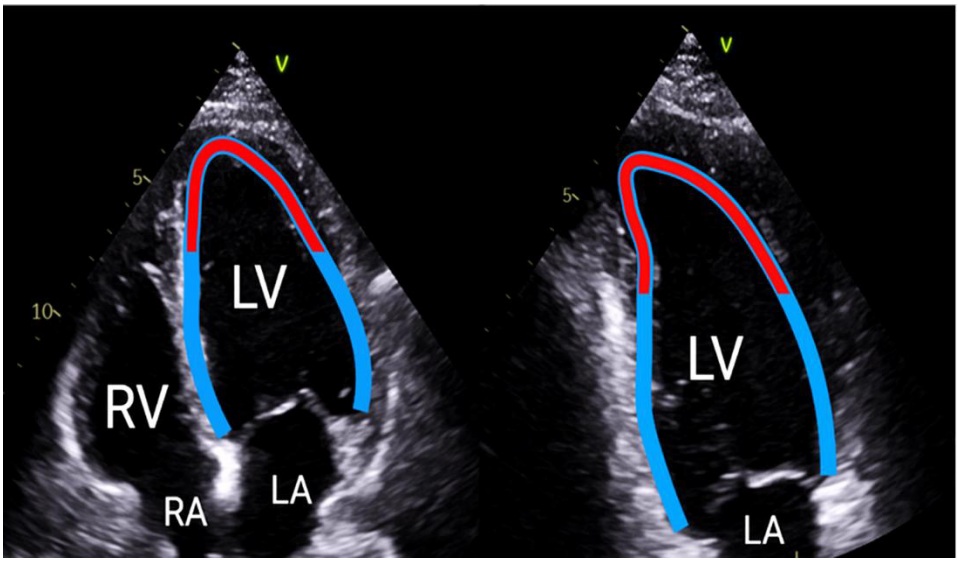


Figure 8: Assessment of akinesia in apical four- (left) and two-chamber (right) views. The LV endocardial length was measured in diastole (blue line), and the extent of akinetic myocardium was outlined and measured (red line). Total akinesia was expressed as the percentage of akinetic length relative to total ventricular length across both views. RA, right atrium; RV, right ventricle; LV, left ventricle; LA, left atrium. Created with BioRender.com.

Correlations between quantitative indices were assessed using Pearson correlation coefficients. The coefficient of variation was additionally calculated to quantify measurement variability. Statistical significance was defined as a two-sided p-value <0.05.

STUDY II

Population

Women with TS and women with anterior STEMI enrolled in the STAMI cohort with serial echocardiographic examinations were included.

Methodological Focus

Serial echocardiographic assessments of LV ejection fraction (LVEF) and PrA were performed at baseline and at days 1–3, 7, 14, and 30. PrA was measured as described in **Study I**.

The primary outcome was stunning resolution at 3 days. Stunning resolution was calculated as the proportion of early recovery of akinesia relative to the total recovery observed during follow-up, according to the following formula:

$$StunningRes_{3days} = \frac{PrA_{Baseline} - PrA_{3days}}{PrA_{Baseline} - PrA_{14days}}$$

Prespecified secondary outcomes included temporal changes in LVEF, global longitudinal strain (GLS), WMSI, tricuspid annular plane systolic excursion (TAPSE), cardiac biomarkers (troponin-I, troponin-T, and NT-proBNP), and biomarker ratios, including NT-proBNP/troponin-I or T, and troponin-I/troponin-T.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range) for skewed variables. Categorical variables are reported as counts and percentages.

The primary analysis compared the resolution of myocardial stunning between women with TS and women with anterior STEMI. Temporal changes in akinesia were modeled using Tobit mixed-effects regression models to account for the zero-inflated, left-censored distribution of PrA values. Time was included as a categorical fixed effect, and patient-specific trajectories were modeled using random intercepts.

Stunning resolution for the median patient was estimated from the fitted models via posterior sampling via Markov Chain Monte Carlo simulations.

Differences between groups were expressed with corresponding 95% credible intervals.

Temporal changes in echocardiographic and laboratory variables were analyzed using mixed-effects linear regression models with time as a categorical fixed effect and patient-specific random intercepts. Variables with skewed distributions were analyzed after logarithmic transformation. Models were adjusted for age, body mass index, diabetes, hypertension, and chronic obstructive pulmonary disease.

All analyses were performed using R version 4.4.1.

STUDY III

Population

Men and women with anterior STEMI enrolled in the STAMI cohort with available serial echocardiographic examinations were included.

Methodological Focus

PrA was quantified as described in Study I. The primary outcome was the resolution of myocardial stunning at the specified follow-up time points, defined as the change in the percentage of akinesia from baseline to follow-up.

$$\textbf{Akinesia recovery} = \textbf{PrA\_baseline} - \textbf{PrA\_T}$$

Stunning resolution was calculated as the proportion of early akinesia recovery relative to the total recovery observed during the follow-up period, following the predefined formula described in **study II.** As a sensitivity analysis, recovery was also expressed as the **proportion of recovered akinesia,** calculated as:

$$\textit{Proportion of recovered akinesia} = 1 - (\textit{PrA\_T} / \textit{PrA\_baseline})$$

where *T* represents the time point of recovery assessment.

Prespecified secondary outcomes included changes over time in LVEF, GLS, WMSI, TAPSE, cardiac biomarkers (troponin-I, troponin-T, and NT-proBNP), the troponin-I/troponin-T ratio, NT-proBNP, and the NT-proBNP/troponin-I ratio.

Statistical Analysis

Continuous variables are presented as mean ± SD or median (Q1–Q3), as appropriate. Categorical variables are reported as counts (percentages). Missing akinesia values were partially imputed by carrying forward 0% values when no subsequent non-zero observations were available. Patients with recurrent events were censored at the time of the second event.

Akinesia recovery in men and women with anterior STEMI was analyzed using Tobit mixed-effects models, accounting for zero inflation and left-censoring. Time was included as a fixed categorical variable, with random intercepts for

patient ID. Sex-specific models were fitted to allow differences in trajectories and variability.

Estimates for the median patient at day 30 were derived from 10,000 posterior samples (R package *brms*), and group differences were expressed with 95% credible intervals. Models were adjusted for age (cubic splines), diabetes, hypertension, and COPD.

Sensitivity analyses were conducted in patients with TIMI flow 0–1. The relationship between the NT-proBNP-to-Troponin-I ratio and akinesia recovery was examined using time-by-interaction terms.

Temporal changes in echocardiographic and laboratory variables were analyzed using mixed-effects linear regression, with time as a fixed effect and patient ID as a random intercept, adjusted for the same covariates.

All analyses were performed using R version 4.4.1.

STUDY IV

Population

This sub-study included women with apical TS, women with anterior STEMI, and men with anterior STEMI.

Methodological Focus

The objective was to characterize myocardial deformation and recovery using speckle-tracking echocardiography. Both global and segmental myocardial strain parameters were analyzed to compare deformation in myocardial regions affected by the index event with that of remote myocardium. Echocardiographic images were digitally stored and analyzed offline using dedicated software.

Global Myocardial Strain

Global myocardial deformation was assessed using global longitudinal strain (GLS) and global radial strain (GRS). Myocardial strain reflects the relative change in myocardial length during the cardiac cycle and is calculated as:

$$\frac{L1 - L0}{L0} X\ 100$$

where L1 represents myocardial length at a given time point and L0 the reference length at end-diastole, longitudinal strain values are therefore negative, reflecting myocardial shortening. In contrast, radial strain values are positive, reflecting myocardial thickening.

GLS was derived from standard apical views (four-, three-, and two-chamber) using automated functional imaging. The left ventricle was divided into 17 segments, and GLS was calculated as the average peak longitudinal strain across all segments.

GRS was obtained from parasternal short-axis views at basal, midventricular, and apical levels. The left ventricle was divided into 16 segments, as the apical cap cannot reliably be assessed in short-axis imaging. Radial strain was measured for each segment and averaged to derive GRS.

For both GLS and GRS, the most suitable cardiac cycle was selected, and strain measurements were obtained at end-systole, the point of minimal LV cavity

size. Automated tracking was visually checked and manually adjusted as necessary **Figure 9**.

Segmental Myocardial Strain

Segmental longitudinal and radial strain were analyzed in myocardial regions affected by the index event and in remote myocardium.

In patients with anterior STEMI, longitudinal strain was measured in segments 8, 14, and 17, while radial strain was evaluated in segments 8 and 14. Remote myocardium was represented by segments 4, 5, 10, and 11. In patients with apical TS, segments 13–17 represented affected longitudinal segments, and segments 13–16 represented affected radial segments. Basal segments (1–6) were considered remote myocardium. Since strain analysis requires sinus rhythm, measurements were not performed in patients with arrhythmias such as atrial fibrillation. These observations were treated as missing under a missing-at-random assumption.

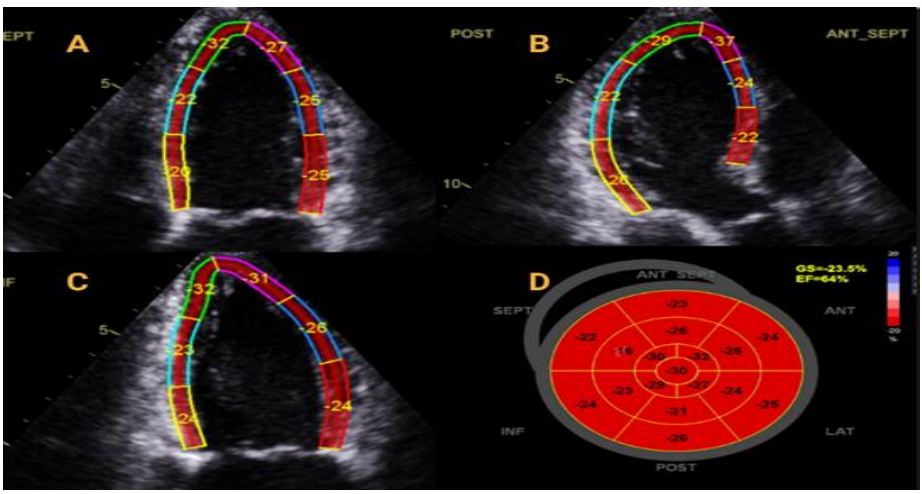


Figure 9: Schematic segmentation of the left ventricle for calculation of segmental and global longitudinal strain obtained from apical views using automated functional imaging. The ventricle is divided into 17 segments, with strain measured in each segment and summarized as global longitudinal strain (GLS). (**A**) apical four-chamber view. (**B**) apical three-chamber view. (**C**) apical two-chamber view. (**D**) bull's-eye plot displaying segmental and global strain values. Reproduced and recreated with permission from Poller A. Available at: https://hdl.handle.net/2077/84037

Statistical Analysis

Continuous variables are presented as mean ± SD or median (Q1–Q3), as appropriate. Categorical variables are reported as counts (percentages).

Temporal changes in GLS, GRS, and segmental strain (affected and remote segments) were analyzed using separate mixed-effects models for TS and STEMI. Time points (days 0, 1, 2, 3, 7, 14, and 30) were treated as categorical fixed effects, with patient-specific random intercepts. Model-derived means with 95% credible intervals were plotted. Patients experiencing a recurrent event were censored from the time of the event onward.

Missing GLS and GRS values were imputed using random forest methods, with segmental values used as mutual predictors. Estimates were pooled according to Rubin's rules.

Associations between myocardial strain parameters and the extent of regional dysfunction (PrA), as defined in Study I, were assessed using Pearson or Spearman correlation coefficients depending on data distribution. Models were adjusted for age, sex, and relevant cardiovascular risk factors.

All statistical analyses were performed with R version 4.2.2.

STUDY V

Population

This sub-study included all patients from the STAMI cohort with TS or STEMI to evaluate LV thrombus formation.

Methodological Focus

The primary objective was to determine the incidence, timing, and predictors of LV thrombus formation following acute cardiac injury and to compare thrombotic risk between TS and STEMI.

LV thrombus was assessed using transthoracic echocardiography as part of the standardized STAMI follow-up protocol. A thrombus was described as an echogenic mass separate from the endocardium, visible in multiple views, and situated in an area of wall motion abnormality **Figure 10.** Thrombi were further classified as mural, when adherent to the ventricular wall with a broad-based attachment and no independent motion, or mobile, when protruding into the ventricular cavity with independent movement.

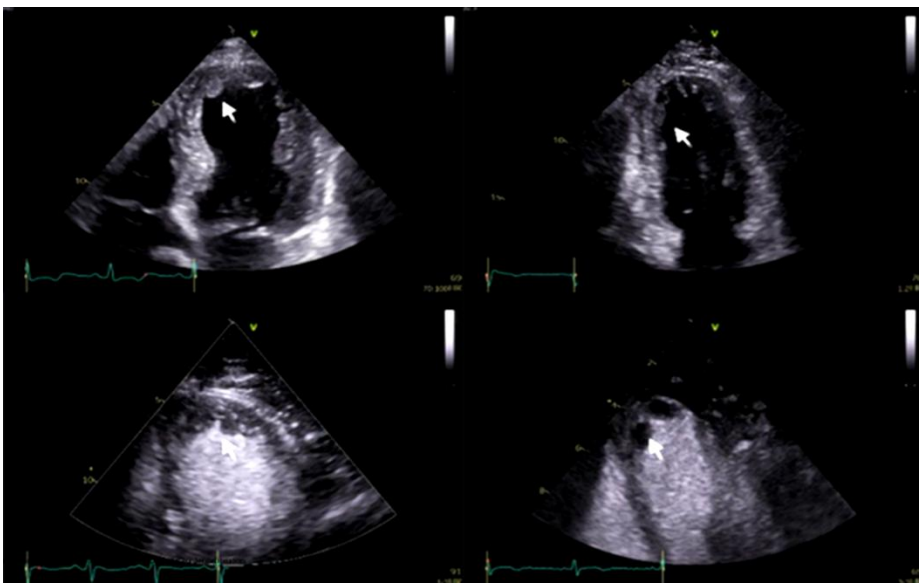


Figure 10: Left ventricular thrombi (arrows) detected by transthoracic echocardiography. Upper panels show non-contrast imaging, while lower panels demonstrate contrast-enhanced visualization.

Regional wall motion abnormalities were quantified using PrA as previously described in **Study I**. Secondary outcomes included thrombus resolution and recovery of regional ventricular function in patients with LV thrombus, compared with those without.

An additional secondary objective was to identify clinical, echocardiographic, and biochemical predictors of LV thrombus formation. Prespecified predictors included indicators of LV systolic function and myocardial injury, such as LVEF, GLS, TAPSE, and serum cardiac biomarkers (troponin-I, troponin-T, and NT-proBNP). Clinical outcomes were systematically assessed during hospitalization and at 30 days and 6 months. Prespecified early outcomes within the first three days included cardiogenic shock, ventricular fibrillation, sustained ventricular tachycardia, and advanced atrioventricular block. Outcomes evaluated at 30 days and 6 months included all-cause mortality, recurrent myocardial infarction, hospitalization for heart failure, stroke or transient ischemic attack, and systemic thromboembolism.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range) for skewed variables. Categorical variables are reported as counts and percentages. Temporal changes in echocardiographic and laboratory parameters were analyzed using mixed-effects linear regression models with time included as a categorical fixed effect and patient-specific random intercepts to account for repeated measurements within individuals. These models were applied to variables with normal distributions (LVEF, GLS, and TAPSE) and to variables that conformed to normality after logarithmic transformation, including troponin-I, troponin-T, NT-proBNP, and biomarker ratios.

Recovery trajectories of regional dysfunction were modeled using mixed-effects models with time as a categorical fixed effect and patient-specific random intercepts. Patients with anterior STEMI with and without LV thrombus were modeled separately to allow group-specific recovery trajectories. Pre-specified predictors of LV thrombus formation were evaluated using Cox proportional hazards regression models. Echocardiographic and biomarker parameters were included as time-varying covariates, whereas clinical variables were included as time-fixed predictors. Missing echocardiographic and biomarker data were handled using two-level predictive mean-matching imputation implemented in the *mice* R package.

All statistical analyses were performed using R version 4.4.1.

STUDY VI

Population

This sub-study included women from the STAMI cohort who had biobanked plasma samples available for proteomic analysis.

Methodological Focus

The goal of this sub-study was to characterize plasma proteomic profiles during the acute and subacute phases of myocardial injury and to identify molecular pathways associated with TS and ischemic myocardial injury.

Plasma samples collected using the standardized STAMI biobanking protocol were used for proteomic analysis. Blood samples obtained during the acute phase (baseline and days 1–3) and the stabilization phase (days 7, 14, and 30) were processed and stored at −80 °C until analysis.

Sample Preparation

Plasma samples were prepared for proteomic analysis using enzymatic digestion protocols optimized for mass spectrometry. Small plasma aliquots were diluted in triethylammonium bicarbonate buffer. Proteins were reduced using dithiothreitol and subsequently alkylated with iodoacetamide to prevent reformation of disulfide bonds. The reaction was quenched with additional dithiothreitol before enzymatic digestion.

Proteins were digested into peptides using a LysC/trypsin combination performed overnight at 37 °C, followed by an additional digestion step to ensure complete peptide generation. Peptide concentration was determined using a fluorometric peptide quantification assay. Before mass spectrometry analysis, peptides were diluted in formic acid and loaded onto Evotips purification cartridges according to the manufacturer's protocol.

Mass Spectrometry Analysis

Proteomic profiling was performed using liquid chromatography coupled with tandem mass spectrometry. Peptide separation was achieved using an Evosep One liquid chromatography system equipped with a C18 analytical column. Mass spectrometric data was acquired using a timsTOF HT instrument with the DIA-PASEF method in data-independent acquisition mode. This technique

enables highly sensitive and consistent detection of peptides across large sample sets.

Protein identification and quantification were performed using Spectronaut software with reference to the SwissProt human protein database. Peptide identification allowed one missed tryptic cleavage, and methionine oxidation and N-terminal acetylation were specified as variable modifications. Carbamidomethylation of cysteine was specified as a fixed modification. Protein quantification was based on MS2-level peptide intensities with automated Cross-run normalization. This workflow facilitates large-scale identification and relative quantification of circulating proteins involved in inflammatory signaling, metabolic pathways, complement activation, and cellular stress responses.

Bioinformatic Analysis

Gene Ontology (GO) enrichment analyses were performed to identify overrepresented biological processes, cellular components, and molecular functions. KEGG pathway enrichment analysis was also performed to identify metabolic and signaling pathways associated with differentially expressed proteins. Enrichment analyses were performed using the ShinyGO platform. A complete set of human protein-coding genes is used as the reference background. False discovery rate (FDR) correction was applied to control for multiple testing. Only pathways with a minimum number of associated proteins and an FDR threshold below 0.05 were considered significant.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range) for skewed variables. Categorical variables are reported as counts and percentages. Differential protein expression between TS and STEMI was evaluated using two-sample and paired t-tests as appropriate. To account for multiple comparisons, false discovery rate correction was applied using the Benjamini–Hochberg procedure, with an FDR threshold of <0.05 considered statistically significant.

Principal component analysis was performed to assess sample clustering and overall data quality. Proteins meeting the predefined significance threshold were subjected to pathway enrichment analyses.

Visualization of differential protein expression was performed using volcano plots generated in R (version 4.2.2).

RESULTS

STUDY-SPECIFIC RESULTS

STUDY I

Population

A total of 140 transthoracic echocardiographic (TTE) examinations from 54 patients were initially available for analysis. 30 TTEs without evidence of wall motion abnormalities were excluded. The final study population comprised 110 TTEs from 39 patients.

Among these, 31 patients (87 TTEs) were diagnosed with STEMI and 8 patients (23 TTEs) with Takotsubo syndrome (TS). Patients with STEMI had a mean age of 64.4 ± 10.7 years; 27 (87%) were male. Patients with TS had a mean age of 57.5 ± 19.8 years; 3 (38%) were male **Figure 11.**

Outcomes

Parameter	Inter-observer bias (Δ ± SD)	Intra-observer bias (Δ ± SD)	ICC (95% CI)	Agreement
PrA (%)	0.52 ± 2.15	0.68 ± 2.87	0.95	Excellent agreement
PrAH (%)	0.47 ± 2.64	0.30 ± 3.99	0.95	Excellent agreement
WMSI	0.03 ± 0.11	−0.06 ± 0.19	0.94	Good agreement

Figure 11: Overview of Study I result. PrA = proportion of akinesia; PrAH = proportion of akinesia and hypokinesia; WMSI = wall motion score index. Values represent mean difference ± SD. Agreement was assessed using limits of agreement, Pearson correlation, and the intraclass correlation coefficient (ICC).

Inter-observer variability: Agreement between observers for the presence versus absence of akinesia was excellent ($\kappa = 0.984$).

For the proportion of akinesia (PrA), mean values were 22.5% ± 12.8% for Observer A and 23.5% ± 12.9% for Observer B. The mean difference between observers was 0.52 ± 2.15, with 95% limits of agreement ranging from −3.69 to 4.75. The Pearson correlation coefficient was 0.986, and the intraclass correlation coefficient (ICC) was 0.993 (95% CI: 0.989–0.995).

For the combined proportion of akinesia and hypokinesia (PrAH), mean values were 32.9% ± 14.3% and 27.5% ± 13.6% for Observer A and B, respectively. The mean difference was 0.47 ± 2.64, with 95% limits of agreement from −4.70 to 5.64. The Pearson correlation coefficient was 0.986, and the ICC was 0.972 (95% CI: 0.959–0.981).

Wall motion score index (WMSI) was 1.65 ± 0.31 for Observer A and 1.62 ± 0.30 for Observer B. The mean difference was 0.03 ± 0.11, with 95% limits of agreement ranging from −0.19 to 0.25. The Pearson correlation coefficient was 0.934, and the ICC was 0.965 (95% CI: 0.949–0.976).

Intra-observer variability: In repeated assessments performed at least one month apart, intra-observer agreement was high. For PrA, the mean difference between measurements was 0.68 ± 2.87, with 95% limits of agreement from −4.96 to 6.31. The Pearson correlation coefficient was 0.972, and the ICC was 0.986 (95% CI: 0.976–0.992).

For PrAH, the mean difference was 0.30 ± 3.99, with 95% limits of agreement ranging from −7.52 to 8.12. The Pearson correlation coefficient was 0.951, and the ICC was 0.984 (95% CI: 0.977–0.989).

For WMSI, the mean difference was −0.06 ± 0.19, with 95% limits of agreement from −0.42 to 0.31. The Pearson correlation coefficient was 0.841, and the ICC was 0.914 (95% CI: 0.875–0.941).

STUDY II

Population

A total of 102 women were included, consisting of 61 with TS and 41 with anterior STEMI. Women with STEMI were slightly older. Chest pain was more common among STEMI patients (97.6%) than among TS patients (55.7%). Among patients with TS, emotional triggers were reported in 45.9%, and physical stressors in 29.5% **Figure 12.**

Outcomes

Total Patients (n = 102)

Baseline characteristics comparable

Metric	TS (n = 61)	STEMI (n = 41)	Interpretation
Akinesia resolution	Slower early recovery	Faster early recovery	Converge at 1 month
LVEF (day 30)	58 %	57 %	No significant difference
GLS (day 30)	-17 %	-17 %	Equal recovery
TAPSE (day 0)	19.8 mm	22.2 mm	Transient RV dysfunction in TS
NT-proBNP	↑	↓	Higher in TS
Troponin	↓	↑	Higher in STEMI

Figure 12: **Overview of Study II results***:* TS = Takotsubo syndrome; STEMI = ST-elevation myocardial infarction; LVEF = Left ventricular ejection fraction; GLS = Global longitudinal strain; TAPSE = Tricuspid annular plane systolic excursion; Arrows indicate relative differences (↑/↓)

The primary outcome, defined as resolution of myocardial stunning at day 3, did not differ statistically between groups. Median stunning resolution was 40.4% (95% CI, 30.1–50.1) in TS and 54.7% (95% CI, 38.3–72.0) in STEMI, corresponding to a difference of 14.3% (95% CI, −4.6 to 34.3). These findings were consistent after multivariable adjustment (adjusted difference: 17.0%; 95% CI, −2.6 to 38.0). Similar results were observed in age-stratified analyses (<70 and ≥70 years). At day 30, all women with TS had complete resolution of akinesia, whereas 49.1% of women with anterior STEMI achieved complete

recovery. Serial assessments demonstrated progressive improvement in LV function in both groups across all time points, including beyond day 7. Patterns were consistent across age subgroups. RV function, assessed by TAPSE, was more frequently reduced at baseline in TS but improved during follow-up.

Peak TnI and TnT levels were lower in TS compared with STEMI. The TnI/TnT ratio was also lower in TS. In contrast, NT-proBNP levels, as well as the NT-proBNP/TnT and NT-proBNP/TnI ratios, were higher in TS than in STEMI.

Clinical outcomes

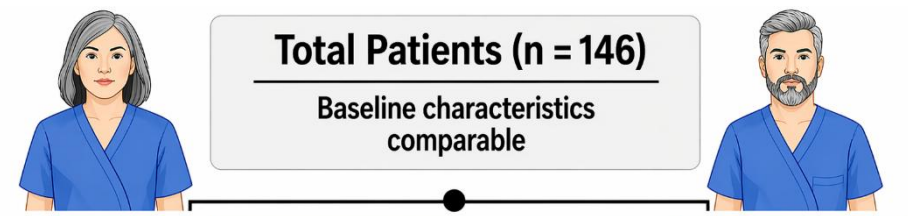
Clinical event rates at 30 days were low and largely similar between anterior STEMI and Takotsubo syndrome. Cardiogenic shock within 3 days occurred in 12.2% of STEMI patients and 14.8% of TS patients. No deaths were observed in either group. Reinfarction and rehospitalization were rare and occurred only in STEMI (2.4% each), while no cases of stroke/TIA or thromboembolism were reported in either group.

STUDY III

Population

A total of 146 patients with anterior STEMI were included, comprising 41 women and 105 men. Women were older than men at presentation (70.0 ± 11.1 vs 63.9 ± 11.2 years). Baseline cardiovascular risk factors, including diabetes, hypertension, and smoking status, were broadly comparable between groups **Figure 13**.

Outcomes



Metric	Women (n = 41)	Men (n=105)	Interpretation
Akinesia recovery	More reversible akinesia	Less reversible akinesia	Greater recovery in women
WMSI	Greater	Smaller	Greater improvement in women
LVEF & GLS	Nominally greater improvement	Improvement	Similar trends
NT-proBNP	↑	↓	Higher in women
Troponin	↓	↑	Higher in men

***Figure 13**: **Overview** **of Study III results**. STEMI = ST-elevation myocardial infarction; WMSI = Wall motion score index; LVEF = Left ventricular ejection fraction; GLS = Global longitudinal strain; TAPSE = Tricuspid annular plane systolic excursion; Arrows indicate relative differences (↑/↓)*

Women demonstrated a greater degree of reversible akinesia compared with men. Although women presented with a slightly larger extent of akinesia at baseline, they had less residual akinesia at 30 days. The proportion of recovered akinesia was higher in women, and a greater proportion of women had complete resolution of akinesia at 30 days.

In the primary model, the posterior probability that akinesia recovery was greater in women than in men was 99.0% at 14 days and 96.0% at 30 days.

These findings were consistent in the subgroup of patients presenting with TIMI flow grade 0/1.

Women showed greater improvement in WMSI compared with men, with posterior probabilities of greater improvement of 99.8% at 14 days and 98.7% at 30 days. For LVEF and GLS, similar patterns were observed, with nominally greater improvement from baseline in women than in men. Left ventricular function continued to improve beyond 7 days in both groups.

Peak troponin-I and troponin-T levels were slightly lower in women than in men, whereas NT-proBNP levels were higher in women.

Clinical outcomes

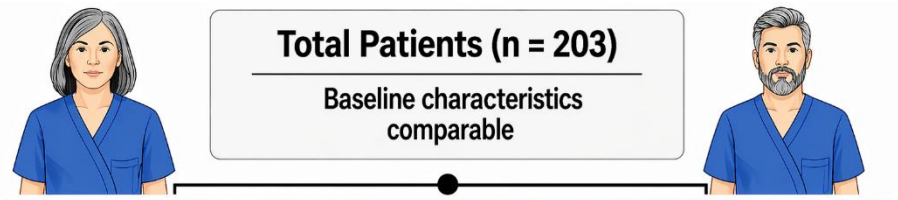
No deaths occurred among women, whereas three deaths were observed among men during the study period. Sustained ventricular tachycardia and ventricular fibrillation were uncommon but occurred more frequently in men. Reinfarction within 30 days occurred in 1/41 (2.4%) women and 2/105 (1.9%) in men.

STUDY IV

Population

A total of 203 patients were included in the strain analysis: 57 women with apical TS, 41 women with anterior STEMI, and 105 men with anterior STEMI. Emotional triggers were reported in approximately half of the TS cases, whereas physical stressors were also common. Baseline clinical characteristics were broadly comparable between groups **Figure 14**.

Outcomes



Metric	TS (n = 57)	STEMI (Women) (n = 41)	STEMI (Men) (n = 105)	Interpretation
GLS (baseline)	More impaired	Less impaired	Less impaired	TS lowest GLS
GLS recovery	↑↑↑	↑↑	↑↑	Greatest in TS
GRS (baseline)	Similar	Similar	Similar	No difference
GRS recovery	↑↑↑	↑↑	↑↑	Greatest in TS
Segmental LS (affected)	Reduced → improves	Reduced → improves	Reduced → improves	Improvement in all
Segmental LS (remote)	More impaired → improves	Less impaired → stable	Less impaired → stable	Recovery mainly in TS
Radial strain	Reduced → improves	Reduced → improves	Reduced → improves	Improvement in all

Figure 14: **Overview of Study IV results**. TS = Takotsubo syndrome; STEMI = ST-elevation myocardial infarction; GLS = global longitudinal strain; GRS = global radial strain; LS = longitudinal strain. Directional arrows (↑) represent relative increases over time. Text descriptors indicate qualitative changes in strain parameters from baseline to follow-up. Arrows indicate relative differences (↑/↓)

Global strain was estimated with 95% credible intervals for GLS and GRS at each follow-up time point. At admission, GLS was significantly more impaired in women with TS compared with women and men with anterior STEMI. GLS was −9.3% (95% CI −10.4 to −8.3) in TS, compared with −11.9% (−13.1 to −10.6) in women with STEMI and −11.7% (−12.5 to −10.9) in men with STEMI ($p = 0.002$ and $p = 0.0004$). No significant difference in GLS was observed between women and men with STEMI. GLS improved significantly between admission and day 30 in all groups, with the greatest improvement

observed in TS (Δ 7.8%), followed by women with STEMI (Δ 4.1%) and men with STEMI (Δ 3.0%).

GRS did not differ between groups at admission but increased significantly during follow-up in all groups, with the largest improvement observed in TS.

Segmental longitudinal strain was reduced in affected segments in both TS and STEMI patients. In remote segments, longitudinal strain was more impaired in women with TS than in women with STEMI at admission. During follow-up, longitudinal strain in remote segments improved significantly in TS but not in STEMI. In affected segments, longitudinal strain improved significantly between admission and day 30 in all groups. Segmental radial strain was reduced in affected segments in all groups and improved significantly between admission and day 30 in both affected and remote segments.

STUDY V

Population:

A total of 314 patients were included: 68 with TS, 148 with anterior STEMI, and 98 with non-anterior STEMI. Baseline clinical characteristics were broadly comparable between groups **Figure 15**.

Outcome

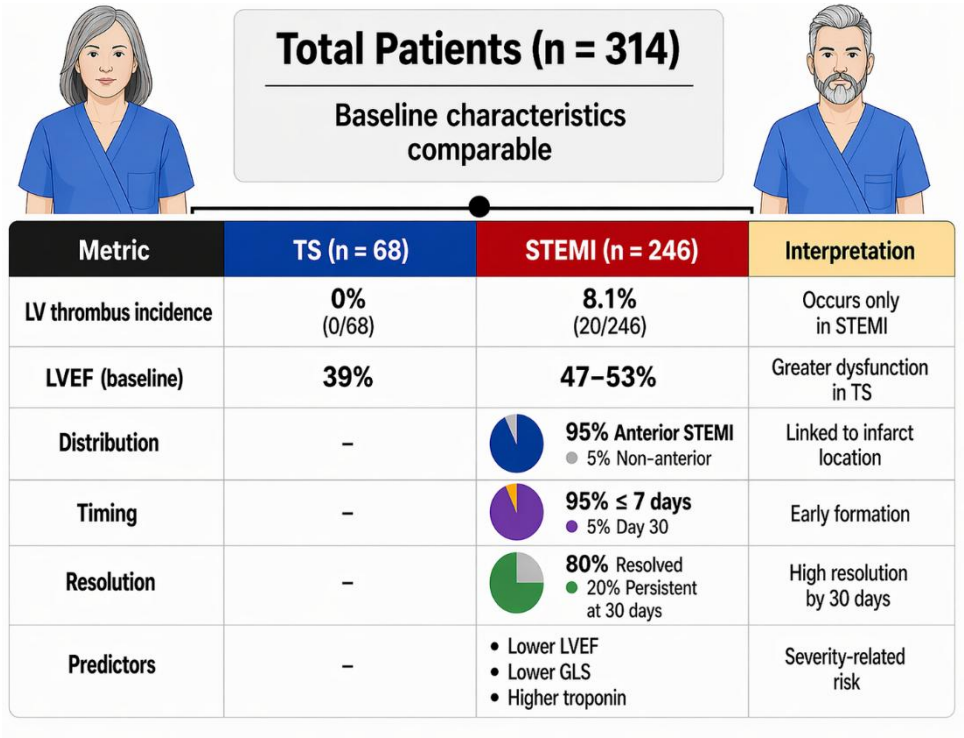


Figure 15: **Overview of Study V results**: TS = Takotsubo syndrome; STEMI, ST-elevation myocardial infarction; LVEF = Left ventricular ejection fraction; GLS, global longitudinal strain

No cases of LV thrombus were observed among patients with TS. In contrast, LV thrombus developed in 20 of 246 patients with STEMI (8.1%). Thrombus formation occurred almost exclusively in patients with anterior STEMI, with only one case occurring in a non-anterior infarction. The majority of thrombi were detected within the first 7 days following the index event. Serial imaging demonstrated that approximately 80% of thrombi resolved by day 30.

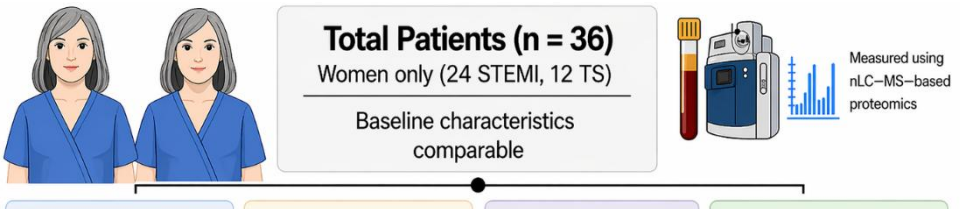
Patients who developed LV thrombus had more extensive myocardial akinesia at presentation. Baseline LVEF was lower in thrombus-positive patients (37.4%) than in those without thrombus (40.1%). LV function also remained more impaired at day 30 (45.3% vs. higher values in thrombus-negative patients).

Similarly, GLS remained more impaired among patients who developed LV thrombus. Higher peak troponin concentrations were independently associated with thrombus formation, indicating a relationship between infarct size and thrombotic risk.

STUDY VI

Population: The proteomic study included 36 women (24 STEMI, 12 TS). Baseline characteristics were broadly comparable between groups. Hypertension and the need for supplemental oxygen were more frequent in TS, whereas smoking and COPD were more prevalent in STEMI. **Figure 16**.

Outcomes



A Between-Group Comparisons: STEMI vs TS

Protein	Acute Phase (Days 0–3)	Stabilization Phase (Days 7, 14, 30)
Inflammation & Injury		
CKM	↑	↑
CRP	↑	↑
SAA1	↑	↑
Complement Activation		
C3	↑	↑
LCN2	↑	↑
HP	↑	↑
Lipid Metabolism		
APOB	↓	↓
PLTP	↓	↓
Repair & Remodeling		
HAP1 (Clusterin)	–	↓
Metabolic Regulation		
ADIPOQ	↓	↓

B Temporal Changes in STEMI
Acute Phase → Stabilization Phase

Proteins	Direction
CRP, SAA1, HP	↑
CKM, C3	↑
LCN2	↑
APOB, APOM, PLTP	↓
HAP1 (Clusterin)	↑
ADIPOQ	↓

C Temporal Changes in TS
Acute Phase → Stabilization Phase

Proteins	Direction
CRP, SAA1, HP	↑
C3	↓
LCN2	–
APOB, APOM, PLTP	↓
HAP1 (Clusterin)	↑
ADIPOQ	↑

***Figure 16*: Overview** of **proteomic changes across different phases.**

Protein Identification and Filtering: A total of 735 proteins were initially identified and quantified. After filtering for missingness, the number of proteins included varied by analysis: 467 proteins in the acute STEMI vs TS comparison, 476 proteins in the stabilization comparison, 485 proteins in paired STEMI analyses, and 460 proteins in paired TS analyses.

Acute-phase proteomics (STEMI vs TS): In the acute phase, 18 proteins were differentially expressed between STEMI and TS, with 12 upregulated and 6 downregulated in STEMI. Upregulated proteins included markers of cellular

injury and inflammation, such as CKM (creatine kinase M-type), as well as complement activation markers, including C6 (complement component 6) and C8A (complement component 8 alpha chain). Additional proteins included PRG4 (proteoglycan 4) and ROBO4 (roundabout guidance receptor 4). Downregulated proteins included markers related to metabolic regulation and tissue remodeling, such as ADIPOQ (adiponectin) and MMP2 (matrix metalloproteinase-2).

Stabilization phase proteomics (STEMI vs TS): During the stabilization phase, 13 proteins were differentially expressed between STEMI and TS, with 3 upregulated and 10 downregulated in STEMI. Upregulated proteins included markers of the acute-phase response and inflammation, such as SAA1 (serum amyloid A1) and HP (haptoglobin), as well as proteins involved in extracellular matrix regulation, including PCOLCE (procollagen C-endopeptidase enhancer 1). Downregulated proteins included those involved in lipid metabolism and lipoprotein remodeling, such as APOM (apolipoprotein M), APOB (apolipoprotein B), and PLTP (phospholipid transfer protein), as well as TFPI (tissue factor pathway inhibitor), a regulator of the coagulation pathway, and ADIPOQ (adiponectin).

Temporal changes within STEMI and TS: Between the acute and stabilization phases, 74 proteins were significantly altered in STEMI (50 upregulated, 24 downregulated) and 25 in TS (13 upregulated, 12 downregulated). In both conditions, upregulated proteins were predominantly markers of the acute-phase response and inflammation, such as CRP (C-reactive protein) and SAA proteins, whereas downregulated proteins were related to complement and coagulation pathways, as well as structural and extracellular matrix components.

Key biomarker: ADIPOQ (adiponectin), a marker of metabolic regulation, was consistently lower in STEMI than in TS during both the acute and stabilization phases.

DISCUSSION

The central finding of this thesis is that myocardial stunning is not a secondary phenomenon in STEMI—it is a dominant and quantifiable component of early ventricular dysfunction(5). The comparison with TS—a condition characterized by profound yet reversible myocardial dysfunction—provides a unique framework for understanding its clinical and biological significance.

Both conditions present with marked acute myocardial dysfunction and exhibit broadly similar recovery trajectories. However, they differ in their underlying biology and complication profiles. By integrating quantitative echocardiography, strain analysis, assessment of thrombus formation, sex-specific comparisons, and proteomic profiling, this thesis demonstrates that myocardial stunning represents a shared functional phenotype across these syndromes, while arising from fundamentally different biological contexts (7).

Methodological Foundation: Quantifying Myocardial Stunning

A fundamental aspect underlying the interpretation of these findings is the methodology used to quantify myocardial dysfunction. In Paper I, semi-quantitative assessment of regional dysfunction using PrA and PrAH demonstrated robust and reproducible measures with good inter- and intra-observer agreement. By translating regional wall motion abnormalities into continuous variables, this approach enabled sensitive detection of both the extent and temporal resolution of myocardial stunning.

This methodological framework underpins all subsequent analyses and strengthens the interpretation that the observed recovery patterns and group differences reflect true biological phenomena rather than measurement variability.

Myocardial Stunning as an Adaptive but Dynamic Process

Myocardial stunning represents a rapid suppression of contractile function during severe cellular stress. Under normal physiological conditions, the contractile apparatus accounts for the majority of myocardial energy consumption, whereas non-contractile processes necessary for cellular survival require considerably less energy. When oxygen delivery is interrupted, mechanical activity ceases within seconds, while cellular energy reserves decline more gradually. By suppressing contraction early, cardiomyocytes conserve energy for essential metabolic processes (4, 11). In this sense, myocardial stunning may represent an adaptive response.

The STAMI data demonstrate that myocardial stunning is not confined to TS but is also a major contributor to myocardial dysfunction in STEMI. Myocardial recovery in anterior STEMI continued throughout the first month following the acute event, indicating that early ventricular impairment reflects not only irreversible necrosis but also a substantial reversible component. These observations suggest that STEMI should be understood as a condition in which necrosis and stunning coexist, rather than as a purely irreversible injury.

Takotsubo Syndrome as the Highly Efficient Form of Stunning

TS supports the concept of a highly efficient form of myocardial stunning. In the STAMI cohort, patients with TS exhibited more extensive akinesia and more severely impaired longitudinal strain than those with anterior STEMI. Despite this pronounced dysfunction, recovery was nearly complete by day 30, systemic inflammatory activation was transient, and thrombotic complications were absent.

This pattern suggests that TS represents a relatively efficient form of myocardial stunning characterized by diffuse but reversible contractile suppression that preserves myocardial viability and allows full restitution of myocardial function. Structural myocardial injury appears limited, ventricular remodeling is minimal, and systemic inflammatory activation resolves rapidly (48, 57, 58).

In contrast, anterior STEMI represents a combination of necrosis and co-existing stunning. Although reversible dysfunction is present and may be substantial, recovery remains incomplete in a subset of patients due to irreversible structural injury. Persistent inflammatory activation and a higher risk of thrombotic complications further distinguish ischemic myocardial injury from stress-induced myocardial dysfunction (57, 59-61).

From this perspective, TS should not be regarded merely as an unusual clinical entity, but rather as a useful reference phenotype against which the reversible component of myocardial dysfunction in STEMI can be better understood.

Temporal Recovery and the Importance of Longitudinal Assessment

A key contribution of the STAMI program is the detailed temporal characterization of myocardial recovery following acute cardiac injury. In both TS and STEMI, improvement in ventricular function extended beyond the first week and continued through day 30.

This finding has important clinical implications. Early post-reperfusion echocardiography may underestimate the degree of reversibility of myocardial dysfunction (60). In anterior STEMI, a substantial proportion of patients demonstrated meaningful improvement between days 1 and 30. In TS, normalization of ventricular function was nearly universal by the end of the first month.

Strain analysis provided further insight into the spatial pattern of myocardial dysfunction. In TS, impairment of global longitudinal strain extended beyond segments with visible wall motion abnormalities, indicating more diffuse myocardial involvement. Despite this widespread dysfunction, recovery was more complete. In contrast, strain impairment in STEMI corresponded more closely to the infarct territory and often remained incomplete during follow-up.

These observations reinforce the concept that myocardial stunning is not a binary phenomenon but rather a dynamic process whose magnitude and duration depend on the nature of the underlying myocardial insult.

Sex-Specific Differences in Stunning Resolution

One notable finding of this thesis is the presence of sex-related differences in myocardial recovery following anterior STEMI. Both men and women exhibited substantial recovery of cardiac function after primary PCI; however, women demonstrated a greater degree of recovery. Despite being older and having a higher burden of comorbidities, women showed more pronounced resolution of akinesia and greater improvement in WMSI during follow-up.

This observation questions traditional beliefs about sex differences in post-STEMI outcomes (51) and indicates that women may have a stronger innate ability to recover from acute left myocardial dysfunction (47, 62).

Myocardial stunning likely plays a key role in this process. Notably, the observed differences were not attributable to typical clinical or procedural factors. Despite having longer delays to reperfusion and more persistent symptoms—which are usually linked to poorer recovery—women showed greater functional improvement. Likewise, variations in coronary flow or the use of guideline-directed medical therapy did not explain the results (63).

Taken together, these results point to underlying biological differences as a key driver of enhanced recovery in women. Potential mechanisms may include sex-related variations in inflammatory signaling, microvascular responses, and

other relevant pathways, including function, hormonal regulation, and cardiometabolic pathways, although these remain to be elucidated. Clinically, these findings emphasize that cardiac function continues to improve during the first 30 days after STEMI in both sexes, with women showing an even greater potential for recovery. This highlights the importance of reassessing ventricular function over time before making long-term management decisions.

Thrombus Formation: Necrosis Rather Than Stunning

The analysis of LV thrombus formation provides an important mechanistic distinction between myocardial stunning and irreversible myocardial injury. Despite more extensive acute LV dysfunction in TS, no thrombi were observed in this group, whereas thrombus formation occurred exclusively in STEMI patients and was predominantly seen in anterior infarctions.

If contractile dysfunction alone were sufficient to generate thrombus through blood stasis, comparable thrombus rates would be expected in TS (53, 54, 64). The absence of thrombus in TS suggests that endothelial injury, necrosis-driven inflammation, and structural remodeling play central roles in thrombus formation. Patients with thrombus-positive STEMI exhibited lower baseline LVEF, more extensive akinesia, impaired GLS, and higher peak troponin levels. Thrombus formation occurred early in the disease course, reinforcing its association with acute infarct-related injury rather than transient stunning alone.

These findings indicate that while myocardial stunning is shared between TS and STEMI, thrombotic risk appears to reflect the extent of structural myocardial injury and the accompanying inflammatory response.

Proteomic Correlates of Divergent Biology

Proteomic profiling provides molecular support for the imaging and clinical observations. STEMI was characterized by sustained activation of inflammatory, complement, and lipid remodeling pathways (57, 60, 61, 65). These molecular signals persisted beyond the acute phase and paralleled incomplete myocardial recovery and the presence of thrombotic complications.

In contrast, TS demonstrated a more transient proteomic response with comparatively attenuated inflammatory activation and more rapid normalization of circulating protein levels.

STRENGTHS AND LIMITATIONS

Several strengths of the STAMI program should be recognized. First, the study was conducted in a prospective, standardized cohort with predefined imaging and biomarker assessments at multiple time points. This approach allowed detailed characterization of the temporal progression of myocardial dysfunction and recovery after acute cardiac injury. Serial imaging with repeated echocardiographic exams enabled quantitative evaluation of myocardial stunning and recovery patterns, something that is seldom available in studies of acute cardiac syndromes.

Second, integrating multiple complementary methodologies is a major strength. The STAMI program combined conventional echocardiography, advanced strain imaging, quantitative assessment of regional dysfunction, clinical outcome analysis, and high-dimensional proteomic profiling. This multimodal approach enabled the investigation of myocardial stunning from structural, functional, and molecular perspectives.

Third, including TS as a comparator condition offered a unique physiological reference cohort. Because TS is characterized by significant but completely reversible myocardial dysfunction in the absence of coronary blockage, it provides a valuable framework for differentiating reversible myocardial stunning from irreversible ischemic damage. Comparing TS and STEMI, therefore, yielded new insights into the relative roles of necrosis and stunning in ischemic myocardial injury.

Fourth, including both women and men allowed for the assessment of sex-related differences in myocardial recovery. Given the underrepresentation of women in many cardiovascular studies, exploring sex-specific recovery patterns is an important contribution.

Several limitations should also be recognized. The STAMI cohort was developed at a single tertiary care center, which may restrict its applicability to other populations or healthcare systems. However, Sahlgrenska University Hospital functions as the main referral center for acute cardiac conditions within a large geographic area, and the patient population likely reflects real-world clinical practice.

Second, although serial imaging was performed according to a set protocol, not all patients completed every follow-up exam. Missing data is common in

longitudinal studies of acute cardiac illness, although statistical models were used to address the incomplete follow-up of repeated measurements.

Third, the observational nature of the STAMI program prevents causal conclusions. The links observed between myocardial dysfunction, biological signaling, and clinical outcomes should therefore be seen as generating hypotheses rather than providing definitive evidence of causal relationships.

Finally, the proteomic analyses were carried out in a relatively small subgroup of patients. While these analyses offered valuable mechanistic insights and produced biologically plausible findings, larger studies will be needed to confirm the molecular pathways identified and assess their clinical importance. Despite these limitations, the STAMI program offers a thorough and integrated characterization of myocardial stunning in acute cardiac syndromes.

CONCLUSION

This thesis shows that myocardial stunning is a key, clinically important part of myocardial dysfunction in TS and STEMI. By systematically comparing these conditions, the STAMI study offers new insights into the extent, timeline, and biological context of myocardial stunning. An overview of the main messages from the STAMI study is summarized in **Figure 17**.

Several key conclusions emerge.

First, significant myocardial stunning occurs in reperfused anterior STEMI. Myocardial dysfunction observed soon after infarction reflects not only irreversible myocardial necrosis but also a substantial reversible component that continues to recover during the first month after the event.

Second, TS represents a phenotype of highly efficient myocardial stunning. Despite severe acute myocardial dysfunction, myocardial recovery is complete, indicating that the underlying myocardial injury fundamentally differs from ischemic necrosis.

Third, recovery of myocardial function is a dynamic process that extends beyond the initial post-reperfusion phase. Serial imaging shows that both global and regional ventricular function may continue to improve in the weeks following acute cardiac injury.

Fourth, biological sex seems to influence myocardial recovery after anterior STEMI, with women showing greater resolution of myocardial stunning compared to men.

Fifth, the presence of LV thrombus is closely linked to ischemic myocardial injury rather than transient contractile dysfunction, as thrombus formation occurred only in STEMI despite more extensive acute dysfunction in TS.

Lastly, proteomic profiling identifies unique molecular signatures between ischemic and stress-related myocardial injury, suggesting that myocardial stunning occurs within different biological contexts depending on the underlying disease mechanism.

These findings collectively support the idea that myocardial stunning is a shared functional phenotype across STEMI and TS. Understanding these differences could improve early imaging interpretation, enhance risk

stratification, and ultimately enable more personalized treatment approaches for patients with acute cardiac syndromes.

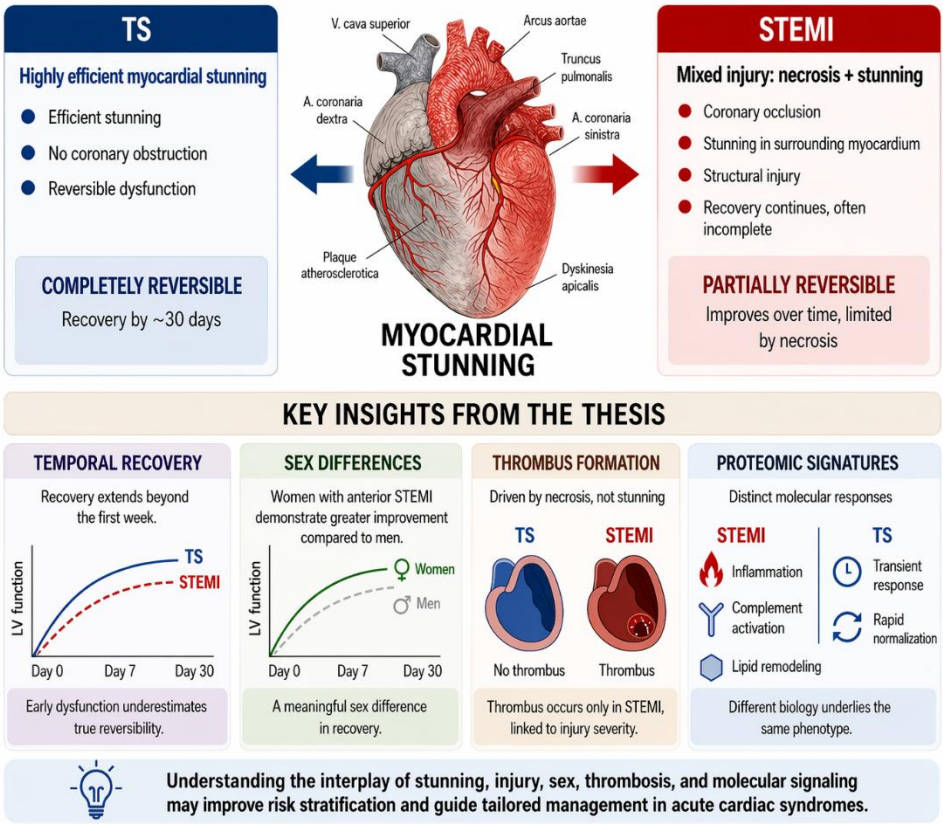


Figure 17: Schematic representation summarizing STAMI take-home message of myocardial stunning as a shared functional phenotype in TS and STEMI, with distinct underlying biological mechanisms and clinical consequences.

ETHICAL CONSIDERATIONS

The STAMI project has been approved by the Swedish Ethical Review Authority (Dnr 2022-01003-02; previous approvals 2019-04092 and 2020-06257). All participants provided written informed consent before participating. The study is conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and the General Data Protection Regulation (GDPR).

All data are pseudonymized using unique study identification numbers. The code key linking study IDs to personal identifiers is securely stored on protected servers at Sahlgrenska University Hospital and is accessible only to authorized personnel. Biobank sampling and storage are performed in accordance with institutional procedures and the Swedish Biobanks Act.

The STAMI protocol and the studies conducted within it do not introduce additional risks to patients beyond normal clinical practice for the treatment of these patients.

Study I analyzed echocardiographic images obtained during routine STAMI assessments and involved no additional procedures.

Studies II–IV relied on serial echocardiography and planned clinical follow-up as specified in the study protocol.

Study V used scheduled echocardiographic examinations to detect LV thrombus—clinical management, including anticoagulation when indicated, followed established guidelines. Follow-up outcomes at 30 days and 6 months were obtained through routine clinical care and secure data collection.

Study VI analyzed biobank plasma samples collected with informed consent. Laboratory analyses were performed on de-identified samples, and the results did not influence clinical decision-making.

Across all studies, risks are limited to routine blood sampling and non-invasive imaging. No experimental drugs or devices are administered. Participants may withdraw from STAMI at any time without affecting their clinical care. Any adverse events possibly related to study procedures are documented and managed in accordance with standard clinical routines and local governance requirements.

FUTURE PERSPECTIVES

The STAMI research program does more than describe recovery after acute cardiac injury; it challenges how we conceptualize myocardial dysfunction itself. The data compels us to reconsider the dominant narrative that early post-infarction ventricular function reflects fixed structural damage. Instead, the findings demonstrate that a substantial proportion of early dysfunction represents a biologically regulated and potentially modifiable state: myocardial stunning.

This thesis has focused on systolic myocardial recovery, especially akinesia, LVEF, and GLS. However, stunning is unlikely to be limited to systolic mechanics. The significant temporal recovery seen up to day 30 raises an important question: Does diastolic dysfunction follow a similar reversible pattern? If so, current ideas about early post-infarction diastolic impairment may need updates. Future studies at STAMI will therefore investigate diastolic strain, atrial mechanics, and ventricular–vascular coupling to see if impaired relaxation and filling are temporary adaptive responses rather than permanent changes.

Similarly, right ventricular (RV) function is unexplored in STAMI. Acute RV dysfunction frequently accompanies anterior STEMI and TS, yet its recovery kinetics and biological determinants are poorly understood. By integrating serial RV strain, coupling indices, and hemodynamic assessment, STAMI offers an opportunity to determine whether RV dysfunction is a parallel manifestation of stunning or an independent determinant of outcomes. This may reshape how biventricular function is evaluated and treated in the acute phase.

A unique strength of STAMI is the integration of serial echocardiography with cardiac magnetic resonance (CMR) imaging in a subset of patients. This multimodality approach provides a rare opportunity to correlate infarct size, myocardial edema, tissue characterization, and myocardial recovery across acute, subacute, and late phases. The ability to disentangle structural injury from reversible dysfunction using both strain mechanics and CMR places STAMI at the intersection of physiology and translational imaging science. These data will allow deeper exploration of how infarct size, microvascular obstruction, inflammatory activation, and hemodynamic adaptation interact over time to determine recovery.

This thesis demonstrates that TS represents a highly efficient and reversible form of myocardial stunning in contrast to the incomplete reversibility of

necrosis combined with superimposed stunning in STEMI. Understanding why stunning resolves almost completely in TS but only partially in STEMI may unlock therapeutic strategies to enhance functional salvage after ischemic injury.

These observational insights can inform experimental design. Animal models of ischemia–reperfusion injury can be refined to incorporate the temporal recovery patterns observed in STAMI, moving beyond static infarct size toward dynamic functional endpoints. The integration of strain imaging, proteomics, and tissue characterization provides a blueprint for translational studies that align experimental biology with human recovery trajectories.

The results have therapeutic implications as current post-infarction management assumes that myocardial function in the first days after STEMI reflects fixed damage. Consequently, the timing of initiation of cardioprotective therapies (e.g., beta-blockers, angiotensin-converting enzyme inhibitors, and SGLT2 inhibitors) is often guided by early LVEF assessment. Yet STAMI demonstrates that myocardial function during this phase is highly dynamic and biologically modulated.

If early dysfunction is predominantly reversible, then the stunned phase may represent a critical therapeutic window. It remains unknown whether initiating cardioprotective therapy during this window enhances recovery and limits maladaptive remodeling, or whether delaying initiation until partial restitution is achieved is superior. The ongoing randomized trial STunning in Acute Myocardial Infarction – Beta blockers, Angiotensin converting enzyme inhibitors and Sodium/glucose cotransporter 2 inhibitors trial (STAMI-BAS), which builds upon STAMI, is the first trial to address this question using high-resolution temporal imaging.

STAMI-BAS aims to test whether early modulation of neurohormonal, metabolic, and inflammatory pathways can influence the trajectory of myocardial stunning. By shifting focus from infarct size alone to dynamic functional biology, we move toward a new paradigm: treating myocardial recovery as an active, modifiable process rather than a passive consequence of reperfusion.

Ultimately, this thesis positions myocardial stunning not as a transient curiosity but as a central biological phenomenon with therapeutic potential. By understanding its mechanisms, kinetics, and efficiency, we may learn not only how to measure recovery but also how to enhance it.

USE OF GENERATIVE AI

Generative artificial intelligence tools, including ChatGPT (OpenAI) and Grammarly, were used during the preparation of this thesis to support language refinement, proofreading, structural editing, and simplification of complex phrasing. The primary purpose of using these tools was to enhance readability, improve linguistic clarity, and ensure consistency and coherence across the included studies. Importantly, all aspects related to study design, data collection, methodology, statistical analysis, results, interpretation, and scientific discussion reflect solely the author's independent work and academic judgment. Generative AI tools were not used for data analysis, hypothesis generation, or scientific decision-making, but strictly as editorial support to improve the overall reading experience.

SCIENTIFIC CONTRIBUTION BEYOND THIS THESIS

Scientific work to which the author contributed during the PhD studies, but is not included in this thesis, is listed below:

Redfors B, **Jha S**, Omerovic E. *Revascularization in Ischemic LV Dysfunction: From Risk to Reality*. **J Soc Cardiovasc** Angiogr Interv. 2025 Aug 19;4(9):103874. doi: 10.1016/j.jscai.2025.103874. PMID: 41040453; PMCID: PMC12485497.

Kakaei Y, Hussain S, Elmahdy A, Berger E, Shekka Espinosa A, Sevastianova V, Sheybani Z, Al-Awar A, Kalani M, **Jha S**, Zulfaj E, Nejat A, Jha A, Pylova T, Krasnikova M, Andersson EA, Silva VRR, Omerovic E, Redfors B. *Comparison of the proteomic landscape in experimental ischemia reperfusion with versus without ischemic preconditioning*. **Sci Rep**. 2025 Apr 7;15(1):11836. doi: 10.1038/s41598-025-90735-4. PMID: 40195349; PMCID: PMC11976975.

Zulfaj E, Nejat A, Haamid A, Espinosa A, Elmahdy A, Pylova T, **Jha S**, Redfors B, Omerovic E. *Temperature and repeated catecholamine surges modulate regional wall motion abnormalities in a rodent takotsubo syndrome model*. **Sci Rep**. 2025 Jan 31;15(1):3876. doi: 10.1038/s41598-025-88410-9. PMID: 39890974; PMCID: PMC11785725.

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RIGHTS AND PERMISSIONS

ACKNOWLEDGEMENT

First and foremost, I would like to express my deepest gratitude to all the patients who participated in this study. Choosing to take part in research at a time of vulnerability requires immense trust, courage, and generosity.

STAMI exists because of you. Your contribution goes far beyond data - it reflects a willingness to help others, even in the most difficult moments. I sincerely hope that what we learn from this work will honour that trust and, in time, improve care for many others.

Behind this work stands a team of individuals whose guidance, support, and dedication made it possible. I would especially like to begin by acknowledging:

Björn Redfors - my main supervisor, mentor, and above all, a very dear friend. You inspire me to pursue clinical research, a path I have never once questioned. Thank you for constantly pushing me forward, encouraging me to improve, and challenging me to think beyond the obvious. You have a rare ability to translate complex concepts into simple, clinically meaningful questions, bridging clinical reasoning and statistics with remarkable clarity. STAMI reflects your vision, an idea you set in motion and continue to nurture with persistence and long-term thinking. Its progress, even through challenging times, is a testament to your dedication and belief in the project.

From our many informal conversations to countless logistics discussions, you show that even the smallest details matter, and somehow make them engaging along the way. I look up to you as a leader in clinical research—grounded, generous, and focused on what truly matters: the patients.

Thank you for your mentorship, your trust, and your friendship—it means more than I can express.

Elmir Omerovic—my co-supervisor. You are a true guru, in the Sanskrit sense of a teacher—someone who inspires confidence and a sense of calm. You're a unique blend of intelligence, humor, and genuine concern for patients. Your passion for cardiology and other topics is infectious. I can't remember a single meeting that felt dull, even if we didn't always start with the most critical questions. You have a rare ability to make medicine and science engaging and meaningful- reminding me that it is not just about finding answers but about asking the right questions and understanding why they matter.

Oskar Angerås and Truls Råmunddal - beyond your roles as co-supervisors, you have been invaluable in shaping my clinical thinking. From interventional cardiology to complex decision-making, I have learned a great deal from both of you. Oskar, you remain my go-to whenever I am in doubt, which, of course, is not very often. Truls, your decisiveness, experience, and clinical instinct are second to none.

Angela - observer no. 1, multi-talented, one of the very best sonographers, and a wonderful human being and friend. Your precision, dedication, and attention to detail have been essential to this work. I have never seen you irritated or overwhelmed, always meeting everything with a smile and a willingness to help. You made even the most demanding days manageable. My thesis would, quite literally, not exist without you.

Rickard and Aaron - both part of the original team that started it all. Rickard, our ethical expert—somewhat involuntarily and the one who coined the name STAMI, is always reliable and a true friend. Aaron, from learning echocardiography as a student to consistently including patients despite a schedule often dominated by the gym—you have been a vital part of STAMI.

Abhishek, Christina, Monica, Sabin, Tetiana, Valentyna, Ermir, Maryna, Mana, Yalda, Linnea, Axel, and Monica—you truly form the backbone of our group. From biobanking and CMR to managing administrative complexities and everything in between, your contributions have been indispensable. Many of you have also stepped in on weekends when needed, showing a level of dedication that goes well beyond what is expected. Much of this work happens quietly behind the scenes, yet it is exactly this effort that keeps everything running smoothly—and, not least, makes me appear far more organized than I actually am.

Sofie and the entire cardiovascular research unit, especially *Anki, Maria, Ida, and Kristina* - your efficiency, patience, and support made what often seemed impossible actually work. I am deeply grateful for all the unseen effort behind this project.

Matilda, Sara, Carlo, Siggi, Emanuele, and Araz - I am fortunate to have such a great group of friends at work. Thank you for the energy, laughter, and all the coffees—you made coming to work something to look forward to. Our many conversations about research and everything beyond it have meant far more to me than you probably realize.

Odd Bech-Hanssen, Björn Wall, and Eva Hagberg, our discussions on myocardial stunning, echocardiography, and life in general have profoundly influenced both my clinical reasoning and my approach to research. The way you bring together deep expertise with thoughtful reflection has been genuinely inspiring, and I have learned immensely from our many conversations.

Sultan, Fati, Tomas, Kevin, Emil, Lars O, and all my other colleagues at Kungälv Hospital—this journey began with you. Kungälv may be a bit small, but it has a remarkably big heart, and it shaped me in ways I deeply value.

A special thank you to all our HIA nurses and, of course, to our cardiology coordinator, Katarina, your ability to quietly hold everything together has been invaluable. What may at times have appeared as disagreements was, in reality, a reflection of a strong bond built on trust, laughter, and a shared sense of purpose.

I would also like to thank the entire team across the Departments of Cardiology at Sahlgrenska, Östra, Mölndal, Varberg, Borås, Skövde, and NÄL, especially all the dedicated healthcare professionals—for your time, support, and genuine interest in clinical research.

To all my friends—*Marlene, Simon, Martin, Sandra, Cecilia* to mention a few—and to *Julia and Jesper*, our essential stop whenever we head south of Gothenburg: you all have been part of this journey somewhere, even if you didn't know it. Those moments—wine, Midsummer by the sea, and simply being together—made life brighter, even after long days and nights of research.

To my dear friends around the world - *Mehul, Snehal, Jasim, Aditi, and Alan* - we started our medical journey together, and somehow it still feels the same after two decades. And honestly, forget the PhD, I might not even be a doctor if it were not for the food Jasim and Mehul fed me.

To my parents—your unwavering support, belief in me, and constant encouragement to strive for better have shaped everything I am today. From you, Dad, I learned the value of hard work and discipline; from you, Mom, the resilience to keep going no matter what—qualities you still gently (and sometimes not so gently) remind me of when questioning how I turned out this way.

To my siblings, Chintu and Mani—you are not only my strength but also my sense of home, no matter where life takes me. And to my wonderful nephews

and nieces, who adore me (as they absolutely should)—you bring joy, energy, and just the right amount of perspective into my life.

Lisbeth, Tage, Malin, and Tommy, my extended family in Sweden - your warmth, generosity, and unwavering support have meant more to me than I can truly put into words. You always step in at a moment's notice and somehow make even my most last-minute requests feel completely reasonable—something I suspect says more about your kindness than my planning. Knowing that I can always rely on you has meant everything, and I am incredibly grateful to have you in my life.

Noah, Liam, and Neil—you are the greatest meaning in my life. There isn't a single day that isn't full of energy because of you three. Many weekends, I took you along to the city so I could keep up with my research—and yes, gelatos were occasionally used as bribes while I did echos and biobanking. Those moments, chaotic and simple, are the ones I will always carry with me.

Lastly, *Josefin* - my other half. You are probably the strongest and most patient person I know, and you have been my constant support through it all.

Living with me during this journey has not been easy - late nights spent disappearing to include patients, endless complaints about being tired, and more than a few disrupted vacation plans. You carried far more than your share, often quietly and without ever asking for anything in return.

I am truly at a loss for words—so I will simply say this:

Everything I am and everything I have achieved rests on you.

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