Takotsubo Cardiomyopathy in a Swedish mixed ICU-population.

A two year follow up of prevalence and short-term outcome.

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Master thesis in Medicine

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Abstract

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Background: A new form of heart failure has recently been described in cardiology, Takotsubo or Stress-induced Cardiomyopathy (TCM). This cardiomyopathy is characterized by a transient, regional myocardial stunning (hypo/akinesis), usually involving the apical parts of the heart. This results in an apical ballooning of the heart with a characteristic shape when visualized. It is often associated with emotional or physical stress. The pathogenesis of this condition is not yet fully known. The current leading hypothesis involves an excess of catecholamines that triggers this regional myocardial stunning. Few studies have been published on TCM in the ICU setting.

Aim: To estimate the prevalence of TCM in a mixed Intensive Care Unit (ICU) population. Further, to describe possible predisposing factors associated with TCM in the ICU, and evaluate if TCM affects ICU outcome.

Methods: This is a retrospective systematic registry study on patients admitted to the ICU at Sahlgrenska University Hospital from January 2011 to December 2012. Electronic health records were accessed through various register programs, such as IVARätt, Melior and LabBest. 3885 patients were included in the study. Every echocardiogram done on patients admitted to the ICU in these two years (n=646) was used as an entry point to find patients with regional hypokinesis. Multivariate analysis was done, in order to find possible predisposing factors, and variables associated with mortality.

Results: 2,1 % of the patients admitted to the ICU during the period from January 2011 to December 2012 were identified with TCM (n=80). Mean age was 63 ± 17 years, with a predominance for women. Parameters significantly associated with TCM were female sex, age, PaO2/FiO2 ratio < 200 and pH < 7,25.
The mortality in the TCM patient population was 36,0 %, as compared to 31,2 % in the general ICU population. TCM and EF < 50 % were associated with increased ICU mortality, even when adjusted for severity of disease. Only EF < 50 % was associated with an increased 90 days mortality.

Conclusions: The prevalence of TCM at Sahlgrenska University Hospital in 2011 and 2012 was 2,1 %. Female sex, age > 60 years, PaO2/FiO2 ratio < 200 and pH < 7,25 were identified as plausible predictors. Further studies would be favoured, to find out more precisely, how these factors are related to TCM. The finding of TCM associated with increased ICU mortality further emphasizes the importance of future research on this subject.

Key Words: Takotsubo Cardiomyopathy, Stress-induced Cardiomyopathy, Intensive Care Unit (ICU)

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1. Introduction

The Takotsubo cardiomyopathy (TCM) was first described in Japan in the beginning of 1990.[i] The cardiomyopathy is characterized by a transient, regional myocardial stunning, usually involving the apical parts, and therefore giving the heart a characteristic shape when visualized. The shape reminds of a Japanese fishing gear for octopus catching (Takotsubo), hence its name. The development of TCM in patients is often associated with a previous exposure to severe mental stress or illness. A genetic predisposition to respond to stress with cardiac failure has been described, further, there is an increased risk with age. The condition predominantly affects women.[ii]

In the literature, TCM is also described as stress-induced cardiomyopathy or the "Broken Heart"-syndrome. *We will use the term TCM to describe the clinical condition in this study.*

The typical patient with TCM shows clinical symptoms resembling an acute myocardial infarction (AMI) such as chest pain, electrocardiographic (ECG) abnormalities and elevated cardiac troponin.[iii] An echocardiogram reveals a regional hypokinesia, commonly misjudged as an occlusion of the left anterior descending (LAD) coronary artery. Often these patients undergo a coronary angiogram, but with no significant stenosis found.

However, patients with TCM may develop severe cardiac failure. With no specific treatment currently existing, patient care is based on supportive modalities such as specific organ support (mechanical heart assistance), intravenous fluids and inotropic drugs. The focus of treating the underlying disease, if recognized, is essential. Recent studies show a significant mortality associated with TCM in its acute phase.[iv] [v] The myocardial condition is, however, fully reversible. If the patient survives the acute phase of heart failure, the long term prognosis is good. [vi]

Our knowledge about TCM is rapidly growing worldwide with an increased number of published articles on the subject. The possible connection between the heart and the brain is an intriguing topic to study, and the field of topic is steadily extending. Despite the progress in our understanding of TCM, there are still many pieces of information missing. Pathogenesis, prevalence, prognosis and treatment are examples of specific areas of interest, in which further research is needed. Is TCM a transient *symptom* equivalent to, for example fever, in which you might need to intervene and treat only in specific rare cases, such as fever-induced seizures in children? Or is it a potentially life threatening condition with need for intervening actions from medical staff, and should it be considered as a strong differential diagnosis in AMI patients?

1.1 Diagnostic criteria for TCM

The current criteria for defining TCM is under debate. Earlier the most common used criteria were *the Mayo Clinic Criteria*. [vii] With increased knowledge on the pathogenesis of the disease these criteria have been questioned and it has now been suggested that these criteria could potentially lead to an underestimation of the severity of this diagnosis. Predominantly because patients that die acutely in TCM and patients with phaeochromocytoma are excluded when using these criteria. [viii] In 2010 a new, more liberal set of criteria were suggested, called *the Gothenburg criteria*.[ix] These criteria included the above mentioned patient groups. Further, it did not require a negative coronary angiogram for diagnosis. Patients who were considered too sick for angiographic procedures and /or who died before undergoing a coronary angiogram were included. The Gothenburg criteria and the Mayo clinic criteria are displayed in the table below. None of the current criteria for TCM are considered as an agreed international standard. The European Society of Cardiology (2010) applied a modified Mayo clinic criteria, adding requirement of the absence of head trauma and intracranial haemorrhage.[x]

Gothenburg criteria [xi]	*Mayo clinic criteria* [xii]
Transient hypokinesis, akinesis, or dyskinesis in the left-ventricular segments and frequently, but not always, a stressful trigger (physical (eg sepsis, subarachnoidal haemorrhage) or emotional).	Transient hypokinesis, akinesis, or dyskinesis in the left-ventricular mid segments, with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
The absence of other pathological conditions (eg, ischemia and myocarditis) that could explain the regional dysfunction.	The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
No or modest elevation of cardiac troponin.	New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
Normal or near normal filling pressure.	The absence of phaeochromocytoma and myocarditis.

1.2 Pathogenesis of TCM

The pathogenesis of TCM is not yet fully understood. Many theories have been suggested, but the full answer of why the heart muscle is stunned for a period of time, nor why it recovers, remains unknown. The definition of TCM includes no visible blood clot in any of the involving coronary arteries, shown in the coronary angiogram, and ischemic coronary disease is not believed to be part of the pathogenesis. There is not sufficient evidence of microvascular ischemia nor decreased perfusion of the heart muscle.

1.2.1 Catecholamine Hypothesis

As of today, the current leading theory is the Catecholamine Hypothesis. It has been shown that serum levels of catecholamines were 2-3 times higher in patients with TCM compared to patients with AMI.[xiii] In addition, it has been shown that intravenous administration of epinephrine and

dobutamine results in symptoms and signs in line with those described in TCM.[xiv] Furthermore, patients with phaeochromocytoma can present with symptoms and signs of TCM.[xv]

The function of catecholamines in the heart is forth-most dependent on its stimulation of β1-adrenoreceptors and β2-adrenoreceptors. These are linked to transmembrane ion channels known as G protein complexes. When the catecholamine binds to its receptor a conformational change occurs in the GS protein. This induces a cAMP-mediated activation of protein Kinase A, resulting in contraction of the heart muscle cell (myocyte).

An excess of catecholamines can affect the G family proteins and alter their state, which results in reduced myocyte contractility. [xvi] An over-stimulation of the G family proteins results in apoptosis of the G protein cells. An evolutionary derivate could be this being a way for the cells to protect themselves. This apoptosis could explain why only a moderate increase of serum troponin levels is observed in TCM patients. This could be compared to AMI patients, where a rather ischaemic-driven process occurs, usually resulting in a higher increase of TNT-levels.

Studies in rabbits show an increased amount of adrenoreceptors in the apical parts of the hearts compared to the base of the heart. This could explain why the apical parts in particular are affected by an excess of catecholamines. It should be noted though, that this has not yet been confirmed in studies done on human hearts. [xvii]

Further, signs of microvascular dysfunction, or dysregulation, in the involved apical parts of the heart has also been seen in TCM patients. This is believed to be a part of the catecholamine hypothesis and is characterized of a diminished vasodilation, an excessive vasoconstriction thus resulting in a reduced myocardial perfusion. [xviii] Inflammation and oxidative stress are believed to play a part in the pathogenesis. [xix]

1.2.2 Ruptured Plaque Hypothesis

Finally, few cardiologists community consider TCM to be an atypical AMI. This theory includes a ruptured plaque in the Left Anterior Descending (LAD) coronary artery, with an appurtenant spontaneous lysis in some cases. [xx] However, studies done on TCM patients show no sign of arterial lesions with neither intravascular ultrasound nor other imaging techniques, rejecting this theory.[xxi]

1.3 TCM and Left Ventricular Dysfunction (LVD) in the ICU setting

With the pathogenesis of TCM in mind, it is interesting to see if patients admitted to the ICU have a higher risk of developing TCM. Patients in the ICU often describe threatening or manifest failure in one or more vital organ systems on admission. Mostly the clinical feature is dominated by an inability to maintain systemic blood pressure and sustain organ perfusion. Therefore, many patients treated in the ICU, for example with severe cardiac failure, are treated with inotropic agents (such as synthetic catecholamines, e.g. Dobutamine) in order to increase cardiac output, among other effects.[xxii] It is not yet known if aggressive treatment with inotropic drugs precipitates TCM. Finally, being admitted to the ICU could be considered a traumatic experience in itself due to the patients loss of autonomy.

Few studies have been published on TCM in the ICU setting. A prevalence of TCM in the ICU of 28 % was reported from South Korea.[xxiii] In another study, with a larger patient population, reported a prevalence of unspecific Left Ventricular Dysfunction (LVD) of 18 %.[xxiv] One of the earlier published articles on TCM patients in the ICU setting is from 2003 where 33 patients were found with myocardial dysfunction over a three year period of time. Median age was 63 years (IQR 23-82) and median Ejection Fraction (EF) was 34 % (IQR 16-48). All included patients improved and normalized their EF and systolic dysfunction with time.[xxv] A more recent study from Turin, published in 2013, found 26 TCM patients in their ICU setting between October 2006 and February 2012.[xxvi] Both studies were, however, using a very strict set of criteria for the diagnosis, which

could explain the discrepancies with other findings. Regarding the clinical features of TCM occurring in ICU patients, a prospective observational study of patients admitted to the ICU (n=6) for non-cardiac disease was published in 2006.[xxvii] They found that the presenting symptom in five out of the six patients, was sudden hemodynamic deterioration requiring vasopressor support.

Global heart failure is a specific form of heart failure that is often seen in the ICU. It is characterized by reduced contractility of all segments of the left ventricle, as opposed to regional heart failure, where only a segment of the heart is affected.[xxviii] It is always secondary to a severe, treatment requiring condition, such as sepsis, uncontrolled hypertension, arrhythmias and metabolic and multi organ insults.[xxix] Global heart failure has been associated with an increased mortality rate.[xxx]

2. Aim

The aim of this study was to estimate the prevalence of Takotsubo Cardiomyopathy in ICU patients, at the ICU, Sahlgrenska University Hospital (SU/S). A secondary objective was to evaluate age, gender, cause for ICU admission, co-morbidites, TNT- and pro-BNP levels as well as average ICU score regarding severity of sickness (SAPS [xxxi], APACHE [xxxii]) as possible risk factors for developing TCM. Finally, we evaluated if TCM affected ICU-mortality.

3. Material and Methods

3.1 Material

This is a retrospective registry study including all patients admitted to the Intensive Care Unit (ICU) at the Sahlgrenska University Hospital from January 2011 to December 2012. The ICU-study population included patients with medical, surgical as well as neurological diagnosis. Patients from

both the Central Intensive Care Unit (CIVA, general ICU population) and the Neuro Intensive Care Unit (NIVA) were included. Patients treated in the Thoracic Intensive Care Unit (TIVA) were excluded from the study, due to their diagnosis being primarily cardiac related diseases. The total amount of patients admitted to the ICU in these two years were 4572. 687 patients were post-operative patients (post-operative care and ICU stay less than 24 hours) and excluded from further analysis. The final amount of patients included in the study was 3885 patients.

3.2 Method

This study was performed as a systematic review of individual Electronic Health Records (EHRs). All 3885 patients were considered for screening and a database was built in *Microsoft Excel*. Through the register program IVARätt information on every patient who underwent an echocardiogram during these two years in the CIVA and the NIVA was obtained. This resulted in a list of 646 patients that was further analysed. Through another register program, Melior, the reports of these echocardiograms made by clinical physiology doctors, were withdrawn. These echocardiogram reports were then thoroughly studied with the specific task of finding heart muscle wall abnormalities and hypokinesia. Any findings regarding this were recorded in the database. Since global heart failure is associated with increased mortality rate, this was registered for the purpose of using these patients as a control group. Right ventricular failure, ejection Fraction (EF) and number of echocardiograms performed were also registered.

Through the database IVARätt, information on age, gender, number of days at the ICU, infusion of one or more vasoactive drugs, was collected for all patients. The cause for admission to the ICU, the defined main diagnosis at the discharge from the ICU, as well as any other comorbidity, were also registered. Further, 90 days mortality and mortality during the ICU admission were registered.

With the register program LabBest we were also able to withdraw information on current TNT levels and pro-BNP levels. These were reported as two values; one of them being the highest reported level of the laboratory test during the admitted time to the hospital, and the other being the highest level of the laboratory test the same day as the current echocardiogram was performed.

When looking at diagnosis that led to admission to the ICU, they were divided into groups based on the same system that is being used by SAPS/APACHE (described in the paragraph below, *SAPS/APAHCE* 3.2.1), and also the current severity of disease scoring system used at the ICU. This way of categorizing the different diagnosis into sub groups based on engaged organ-systems was used because it was a standardized and objective way to categorize these diagnosis. Every patient that is admitted to the ICU receives a cause-to-admission diagnosis. This is standard routine in the ICU SU/S and is a part of the admission process to the ICU. These diagnoses were withdrawn from IVARätt as mentioned above and then categorized according to the built in model in SAPS. See Appendix 1.

Regarding the main diagnose the patients received in the ICU, this was instead set when the patients were discharged from the ICU. In order to present this data in a well-arranged manner, this too, was divided into sub groups. Since this data was registered according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10-SE) system, the very same classification of diseases used in this model was used when dividing our data into sub groups. The purpose of this was to get a standardized way of categorizing diagnoses into reasonable sub groups.

3.2.1 SAPS/APACHE

In order to evaluate severity of illness in patients admitted to the ICU, anaesthesiologists in the ICU use SAPS and APACHE scores for this purpose. These two systems are tools to combine a number of variables on the patient, such as temperature, pulse and blood pressure, into an Estimated

Mortality Rate (EMR) (%) and a score of general sickness, which is expressed as a numerical value. They are tools for the clinicians to make risk assessment. In 2011 APACHE was used in the ICU SU/S. In 2012 the system was changed to SAPS. These two systems differ in the numerical value in the scoring system, but correlates within most of the parameters that they are measuring.[xxxiii xxxiv] These parameters were obtained from IVARätt and included body temperature, Partial pressure of Oxygen in arterial blood (PaO2) from given oxygen treatment, Fraction of Inspired Oxygen (FiO2), PaO2/FiO2 ratio, creatinine, white blood cell count (WBC) and pH from arterial blood gas. Regarding blood pressure, SAPS and APACHE are based on different measures in this parameter. APACHE is based on measuring it as Systolic Blood Pressure (SBP) whereas SAPS is based on measuring it as Mean Arterial Pressure (MAP). In order to merge these two values, they were converted into binary values. In the ICU setting, it is a commonly held notion that a SBP < 90 mmHG is equivalent to a MAP < 60. The blood pressure was considered pathological if the SBP < 90 or if the MAP < 60 and thus given the binary value "1". Values above these levels were considered non-pathological and given the binary value "0". To merge the different scoring values of the general sickness of the patients they were converted into percentiles separately. They were divided into 4 quartiles; 25th percentile, 50th percentile, 75th percentile and 100th percentile. All parameters registered through SAPS/APACHE are income parameters and are generally set within 24 hours of ICU admission.

3.2.2 Acute Myocardial infarction

Since Acute Myocardial Infarction is the major differential diagnosis, this was specifically perused in the journals of every patient with any kind of confirmed hypokinesia on the echocardiograms. The admission entry at the emergency room made by a Medical Doctor (M.D) was examined to see if there was any mentioning of AMI as a differential diagnosis. In the same manner, the discharge note from the hospital was examined. The admission and discharge entry from the ICU was specifically examined. Every journal entry during this admission made by M.Ds on these patients

was examined, in order to find any clues regarding any kind of mentioning of AMI. If a coronary angiogram was done these reports were thoroughly read and noted. If a cardiologist was consulted this was also noted. If a cardiologist assessed symptoms and signs as an AMI this was given a higher level of credibility compared to if a non-cardiologist assessed symptoms and signs as an AMI (with the lack of a positive coronary angiogram regarding LAD occlusion).
This resulted in 4 groups concerning AMI:

1. No AMI – not mentioned anywhere in the journals and/or a negative coronary angiogram
2. AMI confirmed – positive coronary angiogram
3. AMI likely – cardiologist has judged symptoms and signs as an AMI in the absence of objective findings (such as a coronary angiogram)
4. AMI less likely - a non-cardiologist doctor assessed symptoms and signs as an AMI in the absence of objective findings (such as a coronary angiogram)

A history of an earlier AMI and/or current/earlier heart failure was also considered and registered in the database.

3.2.3 Takotsubo Cardiomyopathy

For a patient to be categorized as a Takotsubo Cardiomyopathy (TCM) patient a set of criteria were used, and the patient had to fulfil at least one to be included in the final group of TCM patients:

1. Regional hypokinesis with verified regress* and no current AMI, requiring at least 2 echocardiograms separated in time. No history of earlier heart disease.
2. Regional hypokinesis with no verified regress* (absence of a second echocardiogram) and no current AMI, confirmed with a coronary angiogram. No history of earlier heart disease.

3. Regional hypokinesis with no verified regress* (absence of a second echocardiogram) and no current AMI. No history of earlier heart disease.

*Regress is here defined as regress of hypokinesis.

Since there is no well established international standard regarding the diagnostic criteria for TCM, a synthesis was made and built around the concept of having a transient hypokinesia which could not be explained by a current AMI and with no history of earlier heart disease (earlier AMI, angina pectoris and/or heart failure). These criteria could be considered modified Mayo clinic and Gothenburg criteria. Any significant history of previous cardiac disorder in a patient resulted in that patient being excluded from the TCM group. This approach to the exclusion criteria is supported in analogous studies were prevalence of TCM in the ICU setting were recorded. [xxxv]

4. Statistical methods

4.1 Population and data collection

The data was collected from the hospitals database. All patients admitted to the ICU are consecutively registered, and reported to the department of economical administration as well as the Swedish Intensive Care Quality Register, SIR. This is a standardized routine and plays an important and vital part in generating funds to the hospital as well as generating data for quality control and clinical improvements. For this reason we assume that very little or none data is missing.

4.2 Variables

The variables used were taken from the database built in *Excel*. The variables were divided into sub groups for statistical analysis. The distinguished groups were; all patients, patients who underwent

an echocardiogram, patients identified with TCM and finally, patients identified with general global heart failure (ventricular dysfunction of all involving segments of the heart, as described above). The patients with general global heart failure was used as a control group. Variables such as history of earlier AMI, earlier/current heart failure and associated heart stop were collected as binary values.

4.3 Statistical methods

Statistics was made with the program *SPSS Statistics 21*. Methods that was used were chi-Square, Mann-Whitney u, T-test, logistic regression, Pearson's and Spearman's test.

All parameters were projected as histograms in order to find out if they were normally distributed in the group with all patients, the group of patients that underwent an echocardiogram and the group of patients with TCM, and if they could be considered as parametric data. Everything excluding; days admitted to the ICU, paO2, PaO2/FiO2 ratio, creatinine and WBC were normally distributed and thus classified as parametric data. The above mentioned non-parametric data were revealed as normal distributed when presented as logarithmic values, thus also classified as parametric data in the final analysis. Data that was discontinuous was converted into binary data. This was the case for infusion of 1 or more-, and 2 or more vasoactive agents. T-tests were then done on this parametric data to compare group means and medians to total means and medians. For the converted non-parametric data Mann-Whitney U test was also done to ensure coherence. Values were expressed as either mean values with standard deviation or median values with IQR with percentiles at 25 % and 75 %.

Logistic regression was done as a binary multivariate analysis. Limited by our sample, 8 variables were used as a model. This model was then analysed, based on the likelihood ratio chi-square test,

and variables with weak predictive values were subsequently removed one by one. A Predictive value at 0,1 was set as a cut-off value in the tests of Model Effect.

When doing the Logistic Regression, tests were done to ensure no heavy correlation was present, in order to reveal possible confounders. This was done as Pearson's test for parametric data, and Spearman's test for non-parametric data.

Cross tabs, combined with Fishers exact test was done specifically for the two variables infusion of one or more vasoactive agents, and infusion of two or more vasoactive agents. This was to ensure categorical equivalence.

5. Ethics

Data collecting and patient data management were performed according to the regulations published by the Central Ethical review Board regarding Master Thesis in Medicine at the Gothenburg University. The study was approved by the Head of the Department of Anaesthesiology and Intensive Care Medicine. The main purpose of the study was to make a survey for local improvements of care for patients fulfilling the criteria for TCM. All patient data was decoded using a pseudonymisation process. The code key was kept separated from the database according to the routines at the Department of Anesthesiology and Intensive Care Medicine.

6. Results

6.1 Characteristics of the study group

Total number of patients included in the study were 3885. 646 patients were identified, having an echocardiogram. Following our criteria of TCM classification, 2,1 % of the patients (n=80) were

identified with TCM. These 80 patients were a sub group of the 646 patients that had an echocardiogram. Table 1 describes the detailed characteristics of the whole group (n=3885), the patients who underwent an echocardiogram (n=646) and the patients identified with TCM (n=80).

Table 1. Population Characteristics

	Total (n=3885)	Echocardiogram (n=646)	TCM (n=80)
Gender			
Women	1556 (40.1)	258 (39.9)	46 (57.5)
Men	2329 (59.9)	388 (60.1)	34 (42.5)
Cause of admission *			
Cardiovascular	821 (21.1)	276 (42.7)	21 (26.3)
Liver	164 (4.2)	34 (5.3)	0 (0.0)
Bowel	399 (10.3)	74 (11.5)	11 (13.8)
Neurology	1486 (38.2)	160 (24.8)	31 (38.8)
Trauma	457 (11.8)	71 (11.0)	3 (3.8)
Kidney	49 (1.3)	5 (0.8)	0 (0.0)
Respiration	689 (17.7)	148 (22.9)	10 (12.5)
Haematology	50 (1.3)	15 (2.3)	0 (0.0)
Metabolic	161 (4.1)	35 (5.4)	1 (1.3)
Other	368 (9.5)	19 (2.9)	3 (3.8)
Main Diagnose ICU			
Chock	79 (2.0)	8 (1.2)	2 (2.5)
CVI	616 (15.9)	89 (13.8)	26 (23.9)
Endocrine	94 (2.4)	12 (1.9)	0 (0.0)
Bowel	366 (9.4)	72 (11.1)	8 (10.0)
Intoxication	231 (5.9)	6 (0.9)	0 (0.0)
Cardio	332 (8.5)	149 (23.1)	13 (16.3)
Vascular (e.g. AAA)	205 (5.3)	35 (5.4)	2 (2.5)
Malignancy	126 (3.2)	17 (2.6)	0 (0.0)
Neurology	225 (5.8)	8 (1.2)	0 (0.0)
Kidney	45 (1.2)	6 (0.9)	0 (0.0)
Respiration	405 (10.4)	73 (11.3)	9 (11.3)
Infection/Sepsis	256 (6.6)	75 (11.6)	12 (15.0)
Trauma	567 (14.6)	77 (11.9)	5 (6.3)
Other	338 (8.7)	19 (2.9)	3 (2.8)
Mortality			
ICU Mortality	321 (8.3)	121 (18.7)	19 (23.8)
90 days Mortality	1212 (31.2)	306 (47.4)	36 (45.0)
Ward of origin			
Medicine	1029 (26.5)	267 (41.3)	25 (31.2)
Surgery	1454 (37.4)	234 (36.2)	24 (30.0)
Neurology	1095 (28.2)	114 (17.6)	27 (33.8)
Other	307 (7.9)	31 (4.8)	4 (5.0)
Mean ± StD			
Age	55 ± 22	61 ± 17	63 ± 17
SAPS (N = 2426)	51.0 ± 18.0	59.0 ± 15.8	57.0 ± 15.0
APACHE (N = 2043)	15.0 ± 8.0	20.2 ± 8.8	21.0 ± 9.0
Days admitted to the ICU	3.6 ± 5.9	6.3 ± 8.3	6.0 ± 7.9

Data are n (%) unless otherwise indicated.
*Some patients have several causes of admissions

Out of the 646 patients who did an echocardiogram, 290 patients had any kind of LVD or hypokinesis. 59 patients were identified with global heart failure. 67 patients received the diagnosis AMI, 66 % (n=44) verified with coronary angiogram. 30 % (n=20) were assessed as an AMI by a cardiologist, with the lack of objective findings, and only 4 % (n=3) received the diagnose AMI by a non-cardiologist. 36 patients had a current/history of earlier heart failure and 55 patients had a history of an earlier AMI.

6.2 Population statistics

Table 2 shows the univariate analysis done on all patients, the patients that underwent an echocardiogram, patients identified with TCM and patients with global heart failure.

Table 2.1. Population Statistics, Echocardiogram

	Total (n=3885)	**Echo (n=646)**	*p-value* vs Tot
Mean ± StD			
Age	55 ± 22	61 ± 17	< 0.001
Body temperature (C°)	36.9 ± 1.4	36.8 ± 1.7	0.026
Pulse	97 ± 26	105 ± 28	< 0.001
FiO2 (%)	45 ± 20	54 ± 22	< 0.001
pH	7.34 ± 0.1	7.30 ± 0.1	< 0.001
APACHE score	15 ± 8	20 ± 9	< 0.001
SAPS score	15 ± 8	59 ± 16	< 0.001
EMR (%)	27 ± 23	37 ± 24	< 0.001
EF (%)*	53 ± 13	53 ± 13	
Median (IQR)			
Days admitted to the ICU	1.7 (0.8-3.7)	3.5 (1.7-6.9)	< 0.001
PaO2 (mmHG)	12 (10-16)	12 (10-16)	0.137
PaO2/FiO2 ratio	247 (164-350)	205 (125-300)	< 0.001
Creatinine	84 (65-119)	103 (74-176)	< 0.001
WBC	11 (8-15)	11 (8-16)	0.87
Inf of 1 ≥ vasoactive agents (%)	1612 (41.5 %)	446 (69.0 %)	< 0.001
Inf of 2 ≥ vasoactive agents (%)	632 (16.3 %)	255 (39.5 %)	< 0.001

Echo stands for Echocardiogram.

Table 2.2. Population Statistics, TCM

	Total (n=3885)	**TCM (n=80)**	*p-value* vs Tot	*p-value* vs Echo
Mean ± StD				
Age	55 ± 22	63 ± 17	< 0.001	0.259
Body temperature (C°)	36.9 ± 1.4	36.7 ± 1.4	0.258	0.632
Pulse	97 ± 26	103 ± 27	0.045	0.502
FiO2 (%)	53 ± 20	54 ± 20	0.001	0.776
pH	7.34 ± 0.1	7.30 ± 0.1	< 0.001	0.57
APACHE score	15 ± 8	21 ± 9	< 0.001	0.395
SAPS score	51 ± 18	57 ± 15	0.025	0.405
EMR (%)	27 ± 23	33 ± 21	0.312	0.312
EF (%)*	53 ± 13	47 ± 11	< 0.001	< 0.001
Median (IQR)				
Days admitted to the ICU	1.7 (0.8-3.7)	3.4 (1.7-5.9)	< 0.001	0.803
PaO2 (mmHG)	12 (10-16)	11 (9-13)	0.002	0.053
PaO2/FiO2 ratio	247 (164-350)	179 (129-236)	< 0.001	0.108
Creatinine	84 (65-119)	98 (66-169)	00-09-01	0.173
WBC	11 (8-15)	12 (9-16)	0.019	00-02-01
Inf of 1 ≥ vasoactive agents (%)	1612 (41.5 %)	52 (65.0 %)	< 0.001	0.439
Inf of 2 ≥ vasoactive agents (%)	632 (16.3 %)	44 (55.0 %)	< 0.001	0.003

Echo stands for Echocardiogram.

Table 2.3. Population Statistics, Global Heart Failure

	Total (n=3885)	**Global HF (n=59)**	*p-value* vs TCM
Mean ± StD			
Age	55 ± 22	62 ± 16	0.388
Body temperature (C°)	36.9 ± 1.4	36.5 ± 2.0	0.47
Pulse	97 ± 26	111 ± 28	0.123
FiO2 (%)	45 ± 20	59 ± 23	0.228
pH	7.34 ± 0.1	7.30 ± 0.1	0.271
APACHE score	15 ± 8	22 ± 8	0.551
SAPS score	51 ± 18	63 ± 14	0.059
EMR (%)	27 ± 23	43 ± 22	0.067
EF (%)*	53 ± 13	30 ± 20	< 0.001
Median (IQR)			
Days admitted to the ICU	1.7 (0.8-3.7)	3.6 (1.6-5.6)	0.725
PaO2 (mmHG)	12 (10-16)	12 (10-18)	0.071
PaO2/FiO2 ratio	247 (164-350)	191 (125-311)	0.194
Creatinine	84 (65-119)	137 (80-210)	0.091
WBC	11 (8-15)	12 (9-18)	0.73
Inf of 1 ≥ vasoactive agents (%)	1612 (41.5 %)	34 (57.6 %)	0.055
Inf of 2 ≥ vasoactive agents (%)	632 (16.3 %)	42 (71.2 %)	< 0.001

Global HF stands for Global Heart Failure.

6.3 Predictors (Multivariate analysis)

Table 3.1 shows the univariate analysis that was used as originating model for the multivariate analysis.

Table 3.1 Originating Univariate

Parameter	OR	CI 95% Low	CI 95 % High	P-value
Female sex	2.056	1.314	3.219	0.002
Age > 60 years	2.291	1.414	3.711	0.001
Temp > 38.5	0.700	0.281	1.742	0.443
Pulse > 120	1.973	1.158	3.364	0.0125
PaO2 < 8.0	1.383	0.552	3.463	0.489
PaO2/FiO2 ratio < 200	2.621	1.671	4.110	0.00003
Creatinine > 106	1.917	1.216	3.024	0.005
WBC > 15	1.867	1.163	3.001	0.010
pH < 7.25	3.171	1.946	5.167	0.000004
Low blood pressure*	2.119	1.329	3.377	0.002
Inf of 1 ≥ vasoactive agents	2.673	1.681	4.250	0.00003
Inf of 2 ≥ vasoactive agents	6.687	4.267	10.478	1.117

* MAP < 60. SBP < 90 mmhg.

Table 3.2 shows the final model of the multivariate analysis done. Limited by our sample (n=80), 8 parameters were analysed in the final multivariate model. Temp > 38,5 and PaO2 < 8,0 were excluded because they were not significant (p-value > 0,20) in the univariate analysis. Infusion of 1 or more, and two or more vasoactive drugs were excluded as well because they were the only income-dependant variables, meaning they would be the least objective parameters analysed in this model.

Table 3.2 Final Model Multivariate

Parameter	OR	CI 95 % Low	CI 95 % High	P-value
Female sex	2.059	1.312	3.231	0.002
Age > 60 years	1.904	1.163	3.117	0.010
PaO2/FiO2 ratio < 200	1.942	1.205	3.131	0.006
pH < 7.25	2.377	1.422	3.973	0.001

No potential confounders were found.

6.4 Mortality

Table 4.1 shows the univariate analysis that was used as originating model for the multivariate analysis on 90 days mortality.

Table 4.1 Originating Univariate 90 days Mortality

Parameter	OR	CI 95% Low	CI 95 % High	P-value
TCM	1.829	1.171	2.857	0.008
AMI	1.76	1.76	2.854	0.022
EF < 50 %	3.091	3.091	4.247	<0.0001
1st quartile of severity of sickness*	1			<0.0001
2nd quartile of severity of sickness	2.577	1.968	3.373	<0.0001
3rd quartile of severity of sickness	5.215	4.014	6.776	<0.0001
4th quartile of severity of sickness	15.476	11.927	20.083	<0.0001

* 1st quartile of severity of sickness is used as a reference category.

Table 4.2 shows the final model of the multivariate analysis done on 90 days mortality, adjusted for severity of sickness.

Table 4.2 Multivariate 90 days Mortality, adjusted for severity of sickness

Parameter	OR	CI 95% Low	CI 95 % High	P-value
TCM	1.425	0.885	2.295	0.145
AMI	0.698	0.413	1.181	0.18
EF < 50 %	2.103	1.501	2.945	<0.0001

Table 4.3 shows the corresponding univariate analysis that was used as originating model for the multivariate analysis on ICU mortality.

Table 4.3 Originating Univariate ICU Mortality

Parameter	OR	CI 95% Low	CI 95 % High	P-value
TCM	3.61	2.13	6.12	<0.0001
AMI	0.55	0.26	1.18	0.125
EF < 50 %	3.28	2.22	4.86	<0.0001
1st quartile of severity of sickness*	1			<0.0001
2nd quartile of severity of sickness	1.37	0.72	2.63	0.342
3rd quartile of severity of sickness	4.16	2.35	7.37	<0.0001
4th quartile of severity of sickness	18	10.57	30.64	<0.0001

* 1st quartile of severity of sickness is used as a reference category.

Table 4.4 shows the final model of the multivariate analysis done on ICU mortality, adjusted for severity of sickness.

Table 4.4 Multivariate ICU Mortality, adjusted for severity of sickness

Parameter	OR	CI 95% Low	CI 95 % High	P-value
TCM	2.57	1.44	4.57	0.001
EF < 50 %	1.72	1.13	2.61	0.011
AMI	0.8	0.37	1.72	0.562

7. Discussion

The result of this study revealed a prevalence of TCM in the ICU at the Sahlgrenska University Hospital 2011 and 2012 on **2,1 %** (n=80) with a mean age of 63 ± 17 years, on average, 8 years older than the average ICU population (p-value < 0,001). In this study it was found that TCM was significantly more common in women (p-value 0,002), which is supported in earlier studies.[xxxvi] In the TCM group, 46 patients were women (3,0 % of the total amount of women in the study), and 34 were men (1,5 % of the total amount of men in the study). The leading cause to-admission for the TCM patients was neurological cause and the leading main diagnose TCM patients received in the ICU was Cerebrovascular Injury (CVI), including diagnosis such as stroke, subarachnoidal haemorrhage and intra-cerebral haemorrhage. The mortality rate in TCM patients were 36,0 %, as compared to 31,2 % in the general ICU population. This coincides with recent studies done, revealing a significant mortality in the acute phase of the disease, as mentioned in the background in this article. [xxxvii] [xxxviii]

The group with TCM patients were only significantly different from the patients that underwent an echocardiogram in terms of decreased EF (p-value < 0,001), infusion of two or more vasoactive

agents and borderline significant regarding paO2 (p-value 0,053). In all other parameters, the TCM group was not significantly different from the echocardiogram group.

The control group with Global Heart Failure was not significantly different from the TCM group, with the exception of an average of 17 % less EF in the Global Heart Failure group (p-value < 0,001). A higher SAPS score, EMR (%) and WBC were borderline significant parameters.

Parameters significantly associated with TCM were female sex (p-value 0,002), age > 60 years (p-value 0,01), PaO2/FiO2 ratio < 200 (p-value 0,006) and pH < 7,25 (0,001). A strong association with age and gender has been shown in earlier studies.[xxxix] PaO2/FiO2 ratio < 200 associated with TCM, however, is an interesting finding. A low PaO2/FiO2 ratio is an indicator to measure how well the lungs transfer oxygen to the blood, and is sometimes used to evaluate the severity of e.g. pneumonia. This finding could potentially mean that hypoxaemia is a possible predictor for TCM. Further, a pH < 7,25 associated with TCM is likewise noteworthy. If low pH on its own is a mechanism predisposing for TCM, or if its merely a co-existing factor remains unknown.

When analysing 90 days mortality, significantly increased mortality was associated with TCM, AMI, all four quartiles of severity of sickness and EF < 50 % in the univariate analysis. However, after adjusting for the upper two quartiles of severity of sickness, 3rd and 4th quartiles, in the multivariate analysis, only EF < 50 % was significant. EF < 50 % should here be considered as an unspecific heart failure.

Subsequently, when analysing mortality during the ICU admission, significantly increased mortality was associated with TCM, EF < 50 % and all four quartiles of severity of sickness in the univariate analysis. When adjusting for the upper two quartiles of severity of sickness, 3rd and 4th quartiles, in the multivariate analysis TCM and EF < 50 % were significant.

The discrepancies between the TCM-associated 90 days mortality and ICU mortality can be explained by the current studies on TCM showing a significantly increased mortality in the acute phase of the condition, with a good longterm-prognosis.[xl xli xlii] Further, these results show that TCM is associated with higher mortality than both AMI and unspecific heart failure (EF < 50 %) in the ICU setting. Severity of sickness associated with 90 days mortality and ICU mortality in the univariate analysis is conventional and predictable, and should therefore rather be considered as a measurement of the quality of the study method, in terms of internal validity, than a result on its own.

Information on right ventricular failure were collected, but not considered in the final analysis. Peak, and echocardiogram associated enzyme levels of TNT and pro-BNP were excluded from the final analysis since not enough data could be retrieved. Regarding different levels of credibility on setting the diagnose AMI, this was not considered in the analysis. There was the theoretical possibility that symptoms and signs of a patient could be assessed as an AMI by a M.D with discrepancies with objective findings; such as a lack of significant ST-elevations on electrocardiograms with verified regress of hypokinesis on an echocardiogram and no history of earlier cardiac disorder. This was not the case, and thus not used in any of the analysis.

7.1 Strengths and limitations

The strength of this study was that we were able to study a relatively large sample of ICU patients with none or very few missing data. The final amount of patients included in this study was 3885, however; 687 patients were excluded because they were post operative patients admitted for less than 24 hours. More post operative patients could have been excluded if they would not have been limited by the < 24 h definition. This would have lead to a higher prevalence of identified TCM patients in this material. As mentioned in the background to this report, post operative patients are, by definition, not true ICU patients, and should therefore not be considered in this kind of analysis

when looking at TCM in the ICU setting. However, one could argue that there is a theoretical possibility that a post operative patient could evolve a secondary condition granting them the status of a true ICU patient. The < 24 h definition was set since it is unlikely that a non complicated post operative patient would stay longer in the ICU than 24 h.

The main limitation of this study was finding a standardized definition of TCM that would be applicable to this study. There was a challenge with fulfilling all the current criteria since they required peak enzyme levels, registered electrocardiographic abnormalities, two echocardiograms precisely pinpointed in time, showing a regional hypokinesis on the first one, and a near complete regress on the following one. Further, it required a negative coronary angiogram. There were two problems with strictly following these criteria; firstly, all of these measures were not done on all patients (e.g. coronary angiogram where the procedure was assessed as too risky for the patient). Secondly, they were not always registered and/or there were administrative difficulties reaching them (which was the case in some electrocardiographic reports). This challenge was met by modifying the current most used criteria; the Mayo clinic criteria and the Gothenburg criteria, as mentioned above under “Method and Material”, and excluding all patients with a history of earlier heart disease.

For this reason, our definition of TCM should rather be considered as an indicator for regional hypokinesis with no found genesis, in which TCM *could be* the most plausible cause.

Another limitation of this study was the scoring of the evaluation of severity of illness in patients admitted to the ICU (SAPS/APACHE), since the ICU in Sahlgrenska University Hospital changed their system in 2011/2012 (mid through the study). It would have been desirable to study this group of patients over two recurring years using the same scoring system. However, with the time frame of this project in mind, and the desire to study recent data, the years 2011 and 2012 were favoured.

Using the year 2013 was not possible, since some of the data would have been registered too late. This was the case for the 90 days mortality rate, that would have been registered 31 Mars 2014, which would not have been doable with the time frame of this project.

Another limitation of the present study is that it is a retrospective analysis of patients admitted to the ICU. A prospective analysis of risk factors for TCM would be of value.

7.2 Conclusion and implications

In this study it is concluded that the prevalence of TCM in the ICU at Sahlgrenska University Hospital from January 2011 to December 2012 was 2,1 %. With the findings of the association with increased ICU mortality we conclude that this is a relatively large group of patients worth attention in a mixed ICU population. Regional hypokinesis, as opposed to global heart failure, has earlier not been given much attention, and has in some cases been disregarded as a relevant parameter in assessing critically ill patients. In this study, we show that this approach to regional hypokinesis is deficient. We found a number of possible predictors for the condition, from which age > 60 years, female sex, PaO2/FiO2 ratio < 200 and pH < 7,25 stood out as plausible. If PaO2/FiO2 ratio < 200 and pH < 7,25 are predisposing factors on their own, or if they are solely co-existing factors remains unknown. Further randomized control studies would be favoured, to find out more precisely, how these factors are related to TCM.

The connection between the heart and the brain is as ever intriguing, and further research on the subject is needed to establish the exact mechanisms on why the heart goes into a regional failure, and how it recovers. Unexplained transient, regional heart failures have been found to be present in the ICU, and patient care is based on the clinicians experience of symptomatic, supportive treatment regimes. Future randomized control studies on treatment and management of these patients are needed in order to get standardized treatment guide lines for clinicians.

In the introduction to this article, it was hypothesized around the importance of this condition; whether or not it should be considered a transient symptom, such as fever, rather than a potentially life threatening diagnose on its own. With the findings of significantly increased mortality rate in these patients, compared to the general ICU population, it could be argued as a strong indicator for the latter. Furthermore, it stresses the importance of future research on this subject.

8. Abbreviations

AMI = Acute Myocardial Infarction

ARDS = Acute Respiratory Disease

CIVA = Central-IntensivVårdAvdelningen (Central Intensive Care Unit)

CVI = Cerebrovascular Injury

DIC = Disseminated Intravascular Coagulation

ECG = Electrocardiography (not to be mixed up with an echocardiogram; ultrasound of the heart)

EF = Ejection Fraction

EHR = Electronic Health Record

ICU = Intensive Care Unit

TCM = Takotsubo CardioMyopathy

LVD = Left Ventricular Diesase

M.D = Medical Doctor

NIVA = Neuro-IntensivVårdAvdelningen (Neuro Intensive Care Unit, also called “NICU”)

TIVA = Thorax-IntensivVårdAvdelning (Thoracic Intensive Care Unit)

WBC = White Blood cell Count

9. Populärvetenskaplig sammanfattning (svenska)

I den här studien har vi tittat på en förhållandevis ny beskriven typ av hjärtsvikt, ursprungligen myntad I japan i början av 90-talet. Takotsubo Kardiomyopati, eller ”*Broken Heart Syndrome”* som

den också kallas, är en typ av stressutlöst hjärtsvikt där endast ena delen av hjärtat är påverkat; närmast paralyserat. Detta är ofta kopplat till någon form av fysisk eller emotionell stress. Tillståndet, som ofta initialt påminner om en typisk hjärtinfarkt, är allvarligt i sin akuta fas, men har en mycket god prognos om man överlever denna akuta fas. Hjärtats funktion återhämtar sig i regel fullständigt inom ett par dagar.

Man vet idag inte varför delar av hjärtat paralyseras, men den huvudsakliga nuvarande förklaringsmodellen är att man får ett stresspåslag med ökade nivåer av s.k. katekolaminer (adrenalin är ett exempel på en sådan), som utövar en så kraftig effekt på hjärtat att det paralyseras. Man vet idag heller inte hur patienter med detta tillstånd ska handläggas inom sjukvården på bästa sätt, samt vilken behandling som är mest effektiv.

Vi har studerat denna typ av hjärtsvikt på IntensivVårdsAvdelningen (IVA) på Sahlgrenska sjukhuset, och tagit reda på hur vanligt förekommande detta tillstånd är där, samt om det finns något utmärkande med de patienter som har detta tillstånd. Detta har vi gjort genom att ta del av och studerat journaler, utlåtanden och labb-listor ingående, under en tvåårsperiod, 2011-2012.

Vi fann att 2,1 % av alla patienter som legat på IVA hade det här tillståndet, dvs totalt 80 patienter. Det var vanligare förekommande hos kvinnor och genomsnittsåldern var 63 år. 36,0 % av patienterna med denna typ av hjärtsvikt avled, jämfört med 31,2 % av hela gruppen av IVA-patienter som avled. Vi fann att detta tillstånd var kopplat till ökad dödlighet under IVA-vistelsen. Det var farligare att ha diagnosen Takotsubo Kardiomyopati än hjärtinfarkt på IVA.

Vi fann också att ålder över 60 år, kvinnligt kön, PaO_2/FiO_2-kvot < 200 (en antydan om att lungans kapacitet att överföra syrgas till blodet inte fungerar) och pH < 7,25 (ett lågt pH betyder att blodet är surt) var associerat med detta tillstånd. Det behövs mer forskning för mer exakt ta reda på hur

dessa faktorer är kopplat till denna typ av hjärtsvikt.

Våra resultat pekar på att Takotsubo Kardiomyopati är ett potentiellt livsfarligt tillstånd där mer än en tredjedel av de patienter som vi identifierade med detta tillstånd avled. Vi såg att detta ver kopplat till ökad dödlighet under IVA-vistelsen. Detta poängterar betydelsen av ytterligare forskning i det här området. Det vore önskvärt att, dels identifiera de mekanismer bakom denna tillfälliga paralys av hjärtat, samt etablera och fastställa vilken behandling som är bäst för just dessa patienter.

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11. Appendices

Appendix 1.

SAPS Diagnose groups

1. **Cardiovascular**
    1. Heart Stop
    2. Hypovolemia, non haemorrhage
    3. Hypovolemia, haemorrhage
    4. Septic chock
    5. Cardiogenic chock
    6. Anafylactic chock
    7. Undefined chock
    8. Chest pain

9. Hypertensive crisis
10. Arrhythmia
11. Cardiovascular failure, non-chock
12. Other cardiovascular cause

2. Liver

1. Liver Failure
2. Other live cause

3. Bowel

1. GI bleeding
2. Acute Bowel
3. Pancreatitis
4. Other GI cause

4. Neurology

1. Affected consciousness, Coma to Delirium
2. Cramps
3. Focal neurological loss
4. Intracranial Volume Effect
5. Other neurological cause

5. Trauma

1. Trauma

6. Kidney

1. Renal Failure
2. Pre-renal Failure
3. Post-renal Failure
4. Other renal cause

7. Respiratory

1. ARDS
2. Acute Lung Failure on Chronic
3. Other respiratory cause

8. Haematology

1. DIC
2. Haemolysis

3. Other haematological cause

9. Metabolic

1. Acid- Base- and Electrolyte Disorder
2. Hypo/Hyperthermia
3. Hypo/Hyperglycaemia
4. Other metabolic cause

10. Other

1. Other cause

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