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Does the personality trait of neuroticism cause vulnerability for Takotsubo cardiomyopathy?

A literature review

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Preface

The journey started during our third year of medical school, contemplating about possible topics. We considered different issues related to several medical fields, and then contacted professionals for each field. Some of them we met, and others only replied on emails. Finally, we found our current supervisors. A combination of our curiosity and their engagement for Takotsubo Cardiomyopathy, was conclusive for choice of the topic. The idea of this cardiomyopathy was introduced to us from different sources, through a friend for one of us and through practical clinical tuition for the other. The subject was relatively new, interesting, with limited amount of research available. Further on, Takotsubo Cardiomyopathy was explored, and we observed that many studies linked it to stress, but few emphasized the contribution of personality traits. This became our research question.

The aim of the study was to assess if the personality trait of neuroticism, can increase the vulnerability for Takotsubo cardiomyopathy. Many studies have related takotsubo to psychological stress, but is the personality even more crucial?

Our thesis did not require any financial support nor any formal approval from any institution, and therefore no additional applications were needed. There was no access to personal data, neither could the information obtained from the research articles, identify the individuals.

The thesis is written in collaboration. The 5 graded articles were distributed, two each, and then reviewed by the other person. The last one was analyzed together.

We want to express our gratitude to our supervisors Assami Rösner and Christen Peder Dahl for their support, engagement and steady counseling during the work of this thesis. We would also mention Eirik Reierth, Dr. Scient. Senior academic librarian, at Science and Health Library, who guided us to accomplish a thorough search in the databases. Many thanks to everyone who supported us and lead us through all ups and downs.

Ronja Kamilla Kjær   Sanna Zaman

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Summary

Introduction:

Takotsubo cardiomyopathy (TTC) is a transient left ventricular apical, medial or basal dysfunction, recovering completely without myocardial injury. It was first clinically described in 1991 by Sato et al. Impact of psychological distress and personality factors remains unclear. The aim of the study was to assess if the personality trait of neuroticism, can increase the vulnerability for TTC.

Material and methods:

A systematic literature search was performed in MEDLINE in august 2018, using relevant MeSH terms obtained from PubMed. The search was limited to literature in the time period 2007 – 2018. Study designs included clinical studies, comparative studies, interviews, journal articles, randomized control trials, "reviews" and systematic reviews. 206 records were identified through database searching. After screening of abstracts, 88 articles remained. Selected studies were then assessed for their relevance to the thesis and for scientific quality.

Results:

TTC consists predominantly of postmenopausal women. Presenting symptoms are chest pain and dyspnea. The majority has an emotional stressor combined with a physical or isolated emotional stressor. Anxiety and distress are observed as prominent factors. Though, a correlation between personality type D (PTD) or neuroticism with TTC is incomplete regarding evidence. Most studies underline acute stressful events as a trigger for TTC, while other publications highlight the impact of cumulative stress as more significant.

Conclusion:

The current literature did not show significant correlations between TTC, depression, PTD and neuroticism. However, anxiety has been proven to be a prominent feature. Studies have identified stressful events immediately preceding the acute event. However, some results indicate that exposure to repeated stressful events may have a more decisive role in onset of TTC. Response to distressing factors depends on personality traits, vulnerability and resilience. Nevertheless, more research is needed regarding correlation between neuroticism and TTC.

Explanation of concepts and abbreviations

Takotsubo cardiomyopathy (TTC): A transient left ventricular apical, medial or basal dysfunction most often accompanied by apical ballooning and electrocardiographic (ECG) ST – elevation or T wave inversions. This abnormality is associated with high levels of catecholamines, either administered or endogenously secreted from a tumor or during extreme stress.

Cardiomyopathies: A group of diseases in which the dominant feature is the involvement of the cardiac muscle itself. Cardiomyopathies are classified according to their predominant pathophysiological features (dilated cardiomyopathy; hypertrophic cardiomyopathy, restrictive cardiomyopathy or their etiological/pathological factors (cardiomyopathy, alcoholic, endocardial fibroelastosis)).

Acute coronary syndrome (ACS): An episode of myocardial ischemia that generally lasts longer than a transient anginal episode that ultimately may lead to myocardial infarction.

Coronary vasospasm: Spasm of the large- or medium-sized coronary arteries.

Myocardial stunning: Prolonged dysfunction of the myocardium after a brief episode of severe ischemia, with gradual return of contractile activity.

Myocardial Ischemia: A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary artery disease), to obstruction by a thrombus, or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction).

Myocardial infarction: Necrosis of the myocardial tissue caused by an obstruction of the blood supply to the heart.

Coronary artery disease: Pathological processes of coronary arteries that may derive from a congenital abnormality, atherosclerotic, or non-atherosclerotic cause.

Hypothalamic-pituitary-adrenal axis: HPA-axis.

Catecholamine: A general class of ortho-dihydroxy phenylalkylamines derived from tyrosine. An overall term for epinephrine and norepinephrine, among other terms.

Psychological stress: Stress wherein emotional factors predominate.

Physiological stress: The unfavorable effect of environmental factors (stressors) on the physiological functions of an organism. Prolonged unresolved physiological stress can affect homeostasis of the organism and may lead to damaging or pathological conditions.

Autonomic nervous system: The enteric nervous system; parasympathetic nervous system and sympathetic nervous system taken together. The autonomic nervous system regulates the internal environment during both peaceful activity and physical or emotional stress. Autonomic activity is controlled and integrated by the central nervous system, especially the hypothalamus and the solitary nucleus, which receive information relayed from visceral afferents.

Glucocorticoids: A group of corticosteroids that affect carbohydrate metabolism (gluconeogenesis, liver glycogen deposition, elevation of blood sugar), inhibit adrenocorticotropic hormone secretion, and possess pronounced anti-inflammatory activity. They also play a role in fat and protein metabolism, maintenance of arterial blood pressure, alteration of the connective tissue response to injury, reduction in the number of circulating lymphocytes, and functioning of the central nervous system.

Personality: Behavior-response patterns that characterize the individual.

Anxiety: Feeling or emotion of dread, apprehension, and an impending disaster but not disabling as with anxiety disorders.

Personality type D (PTD): Behavior pattern characterized by negative emotionality (negative affectivity), an inability to express emotions, and social isolation (social inhibition), which has been linked to greater cardiovascular disease and increased mortality.

Hypochondriasis: Preoccupation with the fear of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.

Neuroticism: A pervasive tendency to experience negative emotional states. Neurotic individuals are more likely to experience anxiety, anger, guilt, major depression and respond poorly to environmental stress. They may also have difficulty controlling urges and delaying gratification. Polymorphisms in the SLC6A4 gene promoter have been identified. This concept is a supplementary term under the overall term anxiety disorders.

All terms are obtained from PubMed

1   Introduction

"Doctor: "Please tell us what happened before your chest pain started?"

"Miss X: "Well I was thinking about terrible things that happened when I was young and I felt pressure in my heart and the emotions all ran to my chest and I couldn't get the images out of my head and my heart couldn't bear it so I felt the terrible pain but I wasn't surprised because, with all the emotion, what else was my heart to do?

"The heart does have emotion, you see…. You don't believe me, do you?""

"When I met Miss X (quoted above), I assumed she had misinterpreted the significance of her emotions in relation to her cardiac symptoms. However, to some degree, she was correct. Whether or not her heart 'has emotion' is perhaps down to semantics (does 'having emotion' require emotion generation or simply sensitivity to emotion?), but medical investigations confirmed that her chest pain was the result of Takotsubo cardiomyopathy broken heart syndrome'. This is a poorly understood condition where intense emotional or physical stress brings about potentially lethal changes to cardiac contractility, changes that are distinctly different from those found in a 'normal' heart attack. For Miss X, extreme emotion threatened to literally 'break' her heart."(1)

1.1   History of Takotsubo Cardiomyopathy

From the early 1990s, Japanese authors described a type of acute, transient and reversible cardiomyopathy, similar to ST elevated acute myocardial infarction (AMI) either in clinical presentation or electrocardiography (ECG) and cardiac parameters. A peculiarity of the syndrome was left ventricular (LV), apical or medium apical segment dyskinesia/akinesia during the acute phase, commonly recovering very rapidly. (2) This clinical phenomenon was first described in Japan by Sato et al. (1) in 1991 and is probably still an underdiagnosed disease. (3) Some other terms used for this condition are stress induced cardiomyopathy, broken heart syndrome, apical ballooning and Takotsubo syndrome. Because of its feature, the syndrome was given the name Takotsubo cardiomyopathy (TTC) which was recalling the shape of a trap used by fishermen to catch octopus. (2) TTC mimics acute coronary syndromes (ACS), but in the absence of obstructive coronary artery disease. Emotional triggers are common, but little is known about the psychological background characteristics

of TTC. (4, 5) Ghadri et al. (2016) refer to recent studies which have shown a connection between TTC and a positive life event, introducing a new term, "happy heart syndrome". (6) This indicates a generalized reaction to stress, independent of positive or negative loaded emotions. Despite extensive research, the cause, pathogenesis and heterogeneity of clinical features is incompletely understood. Particular emphasis has been devoted to the role of the central and autonomic nervous system, and catecholamine surge. (2)

1.2 Laboratory findings

Apart from the extensive wall motion abnormalities in TTC patients, the cardiac biomarkers creatinine kinase (CK) and troponin levels are limitedly elevated, and CK rarely exceeds values above 500U/l. Furthermore, as a result of left ventricular wall stretching, plasma concentrations of brain natriuretic peptide (BNP) are remarkably elevated in patients with TTC compared to ACS patients. (7-12) Although different profiles of cardiac biomarkers are evident, no cut-off values for troponin, CK and BNP have yet been defined as useful for discrimination of TTC and ACS. (13) On the other hand, circulating micro-RNA has been shown to be a potential diagnostic tool in the acute phase to differentiate TTC from STEMI, but this laboratory finding is still not accessible for clinical use. (14)

1.3 Triggering events

In a majority of patients (70-80%) a triggering event can be identified. There are equal distributions of emotional and physical stress in 30-40% of the patients. (15, 16) These data depend on the precision of clinical history taking, which may vary in large registries. In addition, it may also be difficult to differentiate the stressors. (16) Surprisingly, many studies have pointed out that in a great amount of cases, sometimes up to one third of the cases, there are no known triggering event.

1.4 Diagnosis

Guidelines for TTC diagnosis have been presented from various sources, with some differences in inclusion and exclusion criteria. When immersing the literature concerning our topic, we discovered that a worldwide consensus has not yet been established. For example,

most of the prior studies have emphasized that obstructive coronary disease must be excluded. In recent years however, new criteria have been suggested where absence of obstructive coronary disease is no longer excluded. The possibility that TTC and coronary artery disease could coexist is important to remember, as not all patients with TTC have normal arteries. (17) Two international expert consensus documents on TTC have been published. They assert that TTC is a poorly recognized heart disease where current guidelines are lacking, and controversies are present such as nomenclature, different TTC types, role of coronary artery disease and cause. The diagnosis of TTC is often challenging, and a wide range of heterogeneity patterns and clinical presentation of TTC has been acknowledged. (2)

Because of variations in literature concerning the Mayo criteria, all modified versions are considered. Latest proposed guidelines from EHJ (European Heart Journal) 2018 will be presented and reviewed in our discussion.

Figure 1: Angiographic image of a Takotsubo cardiomyopathy (TTC) patient with non –
obstructed coronary vessels.

1.5   Epidemiology

The increasing number of patients referred to coronary angiography with suspected ACS have helped reveal the incidence of TTC. Multiple series have shown that approximately 2% of all

patients presented with ACS symptoms have been identified as TTC. Its incidence is estimated to be 29, 8 per 1,000,000 inhabitants in a global population. (18) The prevalence of TTC is predominated by postmenopausal women, regardless of ethnicity. (19)

1.6   Influence of gender and age

The mean age range of patients with TTC is between 58 and 75 years, and about 90% of the cases occur in women. In all studies reported so far, a large discrepancy in prevalence of TTC between men and women has been established. (11, 20-34) Explanations regarding this is contradictory, and no clear pathophysiological explanation is ascertained. (35) The reason why TTC mainly affect postmenopausal women is not fully understood, but it is proposed that the lack of the cardio protective effect of oestrogen may play an important role.

Gender specific prevalence presenting with ACS symptoms is higher in women ranging from 6 - 9.8%, whereas the prevalence among male patients presented with ACS symptoms is less than 0.5%. (36-38) According to case descriptions, men constitute less than 11% of TTC cases in Western countries. However, the number of male patients in Asia seems to be higher in registry-studies ranging from 13 - 35%. (30, 39, 40) It is currently unclear whether underdiagnosis or misdiagnosis may contribute to the lower prevalence of TTC in men. Furthermore, in addition to lower prevalence in men, it has been reported that men more often experience sudden death in the early phase of TTC. In the case of early death, diagnosis cannot be established because of missing documentation of the typical course of this syndrome including normal coronary arteries and rapid resolution of the wall abnormality. (16) In – hospital mortality has been reported to range from 0 - 8% and is typically reported in the 1 - 2% range. (7, 28, 41, 42) In an inpatient - database from the United States which included 24.701 TTC patients, risk factors and outcome were analysed. Differences in the mortality rate between gender was prominent, were the mortality rate was 2,5 times higher in men than in women. (32, 33) Akashi et al. (2015) also points out that mortality in men seems to be higher than in women according to several studies, but these reports were based on a small sample of patients. (17)

Younger women seem to be occasionally affected. (11, 20-34) Approximately 10% of patients are less than 50 years of age (29, 30), and even young individuals as well as children of both

genders may be affected. Furthermore, there are some case reports of younger females with TTC in the context of normal pregnancy (43) after miscarriage, and after labour or delivery. (44-47) In addition, it is suggested that in the postpartum period women may be at risk of developing TTC because of the abrupt depletion of oestrogen levels after expulsion of the placenta. Also, in particular after caesarean delivery, TTC may be triggered either by an intense emotional and/or physical stress of the simultaneous administration of the catecholamines, which are often used to stimulate uterine contraction. (45)

The youngest known individual affected by TTC was 2 days old and the onset was triggered by foetal distress and hypoxemia. (48) Other children developing TTC are those undergoing surgery or in the context of morphine withdrawal. (49-53) Overall, the triggering factors, presentation, clinical course, ECG and echocardiographic findings are similar in children and adults. (50)

1.7   Genetics

According to the literature reviewed, it seems to be still unknown, if genetics play an important role. Pellicia et al. (2017) noted that mechanisms of myocardial protection seem to act differently in individuals because of genetic variability in general. (54) Several studies analyzing polymorphism potentially involved in the pathogenesis of TTC have demonstrated differences in the various subtypes of both adrenoceptors (55) and oestrogen receptors. (56) A genetic predisposition to TTC might explain why some develop the disease without preceding stressor or are at risk of recurrence. (57) Vriz and colleagues demonstrated an increased genotype frequency of a beta-1 adrenergic receptor (β_1AR) polymorphism (amino acid position 389) in patients with TTC compared to controls, but other researchers could not reproduce these findings. (58) Other genetic polymorphisms such as L41Q and L14 were also suggested, but so far without significant evidence. (59, 60) Larger genetic studies are necessary, the most recent research indicates a genetic vulnerability of adrenergic cell signalling, where the receptors above might play an important role. (61)

1.8   Pathophysiology

The pathophysiology of TTC is not completely understood. (62)

Most recent evidence supports the concept of increased catecholamine concentration in the acute phase of TTC. This might induce direct myocardial injury and coronary spasm, mostly at the microvascular level. Additionally, due to increased cardiac workload which contributes to an acute situation of supply-demand mismatch, it may result in post-ischemic stunning. The functional counterpart at the LV level would be the typical apical ballooning that persists as a result of stunned myocardium, followed by complete functional recovery over relatively short time-periods. (54)

Naegele et al. (2016) has brought additional information to the pathogenesis of TTC. The new concept claims that the condition differs markedly from cardiomyopathies as currently defined. A common factor in patients with TTC is endothelial dysfunction which is a pathological state of the endothelium characterized by an imbalance between vasoconstricting and vasodilating factors. The imbalance mentioned above may represent a link between stress and myocardial dysfunction in TTC. (63)

The common feature of primary (no prior medical cause) and secondary (complication due to medical illness) TTC cases are the surge of catecholamines and enhanced sympathetic activity. This has been central to a better understanding of the syndrome and has through the years led to the term "stress cardiomyopathy". Clinical studies have demonstrated extremely high levels of catecholamines in TTC patients. (5) The serum concentrations of epinephrine (EPI) and norepinephrine (NE) are significantly higher in these patients compared to patients with myocardial infarction (5), and further on they remain elevated. Interestingly, serum half-life of EPI is almost 3 min (64) if TTC is caused by a stressor that triggered a large, but short catecholamine secretion. 24 h later, the plasma EPI concentration should be 480 half-lives lower, with tiny concentrations still circulating. The clinical observations support a prolonged activation of the sympathetic nervous system, combined with molecular and physiological "memory" of the catecholamine storm. (65)

To explore in detail the pathophysiology of TTC, researchers have obtained information from animal models. Ueyama et al. 2002 and 2003, Redfors et al. (2014), Shao et al. (2013) and Paur et al. (2012) to mention some, have studied animal reactions to pharmacological and psychogenic stress. Wright et al. have summarized the results in their review. (65) The

findings below are based on experimental studies performed on rats, monkeys and mice. Both sexes were included, an exogenous dose of catecholamines were administered, and the time frame of observation was 20 min to 10 days. Some studies included intervention, others not. These observations have given us directly insight to the initial symptoms of TTC at a molecular level, in addition to the ongoing hours and days.

1.9   Time course

0-60 seconds:

Plasma levels of catecholamines, and in some cases sympathetic neural activity, elevates rapidly to peak levels within seconds of a stressful trigger or exogenous bolus of intravenous catecholamines. They will bind to alfa (α) and β –adrenergic receptors of all subtypes. More specifically for this case the endothelium and smooth muscle of the vasculature, both coronary and peripheral. The two receptors are G-protein coupled and can rapidly activate the secondary messenger pathways. (65) In a TTC rat model, Paur et al. (2012) showed that a high dose of intravenous EPI bolus given to rats increased the aortic blood pressure extremely within seconds. This in accordance with the sympathetic drive felt by patients within seconds of the stressful trigger. (66) Initially, this is a positive inotropic response throughout the LV myocardium, and peripheral vasoconstriction with rapid elevation of both systolic and diastolic pressures. In addition, Redfors et al. (67) claims that this hypertensive surge can activate a bradycardia reflex, and they recently reported that multiple catecholamines with α-receptor activity, when injected in rats, can induce TTC-like dysfunction. This suggests that acute changes in systemic vascular resistance and aortic pressure may affect the myocardium, resulting in dysfunctional activity. (65)

1-10 minutes:

The data from respective models should be compared with caution because of the pharmacokinetic factors, that may account for these differences. (66, 68) Isolated cardiomyocyte studies show that stimulation of β_1 adrenergic- receptors results in rapid positive inotropy. In contrast any inotropy caused by β_2 adrenergic receptors only occurs in apical cells and only after 5 min. (66, 69) Correlating with this, the activity in vivo is

uncertain. The concept further on illustrates that β_1 receptors are beginning to exert positively inotropic effects via PKA-mediated phosphorylation of downstream effectors. The cardio toxic effects may begin at this. (65) The acute effects upon the coronary vasculature remain to be determined, although studies have failed to show apical perfusion abnormalities during the acute phase. (70)

0-1 Hour the ultra-acute phase:

It is difficult to observe the initial symptoms and changes at the molecular level in a TTC patient. This is due to the time gap between onset and first medical contact. Therefore, many of the cardiovascular parameters are obtained from animal models. (65) Findings at this stage might be sinus tachycardia, hypertension, with pronounced pulse pressure, and ST-segment elevation. (71, 72) Patients report symptoms in the seconds following their stressful trigger consistent with an adrenaline rush or panic attack. (65) ST segment elevation is a commonly reported ECG finding which appears to precede the clinical apical dysfunction and cardiogenic shock. (65) There are also described acute left ventricular outflow obstruction (LVOTO) in this phase (73) which could further on exacerbate the apical dysfunction. This exposes the apex to higher stress compared with the basal myocardium. This high apical wall stress could cause apical ischemia and exceed the catecholaminergic stunning. (74) This was shown in an animal study where low afterload caused increased wall-tension in the apical myocardium because of the LV lumen obliteration. (68) The relevance of LVOTO in majority of TTC patients are probably limited, being prevalent in only 10 - 15% of cases. (75) A subclinical LVOTO may still contribute to the apical dysfunction. (65)
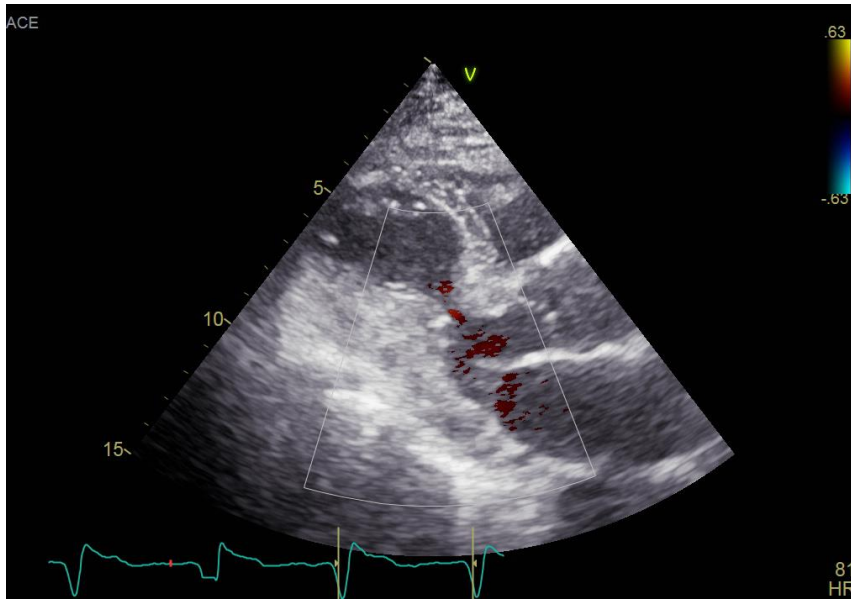
Figure 2: Echocardiography showing left ventricle (LV) in acute phase of Takotsubo cardiomyopathy (TTC) with hyperkinetic base.

1-12 hours:

The clinical presentation may occur many hours, days or weeks after the triggering event(s). The so called textbook TTC patient presents with chest pain, dyspnea and ST-segment elevation. (41, 74) Typically, during angiographic examination the coronary vessels appear unobstructed and the plasma catecholamines are still markedly raised. (5, 76)

24-72 hours:

During this period, a series of molecular, structural and clinical changes may offer clues to the underlying disease process. Nef et al. (2008) found an increased superoxide production in biopsy taken from the TTC patients within 12 hours after admission. These findings were later compared with control samples taken 21 days later, when the cardiac contractility had increased. Superoxide production were associated with increased gene transcription of Nrf2-gene. (77)

On admission, the ejection fraction (EF) was lower than the normal range (42) and remained depressed after 24 hours. (78) In addition, two patterns of ECG was seen in TTC patients; initial ST segment elevation within the first 24 hours, and fragmented QRS complexes. (79)

The evolution in the 24-72-hour period of widespread and deep T wave inversion and significant QT prolongation, compared to the admission ECG is a striking observation. (80, 81) It is debatable that T wave inversion could help differentiate ACS and TTC. Also, the circulating biomarkers showed a NT-pro-BNP raise in plasma from TTC patients after 24 hours compared to NSTEMI and STEMI, whereas Troponin T was only mildly increased. (82)

3-7 days:

In most patients, cardiac function will be improving within 3-4 days, after the onset of TTC. A study using serial ECG showed significantly improved LV-function between day 3 and 7, compared to the admission. Although the catecholamine levels were still raised. (5) This was confirmed in another study where 94 out of 126 patients had normalized LV function at their first follow up within one week. (42) Within hospital mortality is 0,5-1%, most often due to cardiogenic shock and multi organ failure. (83)
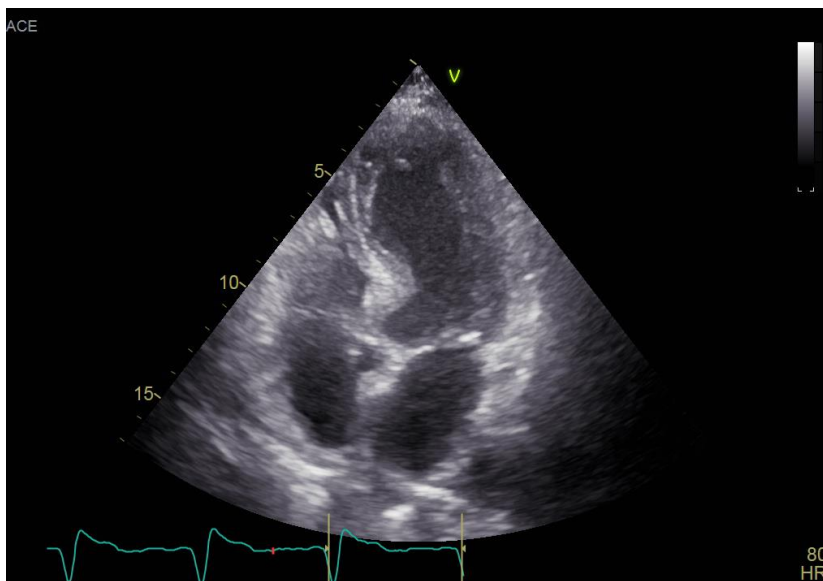
Figure 3: A typical transthoracic echocardiography from a patient with Takotsubo cardiomyopathy (TTC).

1.10 Different types of left ventricular dysfunction

Different types of left ventricular dysfunction and corresponding ballooning patterns have been reported in TTC. These include the classical apical variant, a midventricular variant, a

basal or inverted variant, and other regional variants. (84) The most prominent type is the classical apical variant, which accounts for 80% of the cases. (85) The reported incidence of non-apical variants overall ranges from 8-40%, in different studies. (84, 86, 87) Some unusual cases with involvement of the right ventricle have also been reported.

The heart is densely innervated by sympathetic nerves. Since these nerves follow a regional distribution, it has been hypothesized that the typical apical pattern of LV dysfunction results from this anatomy. (88) This also applies to the regional distribution of sympathetic adrenoceptors. (89)
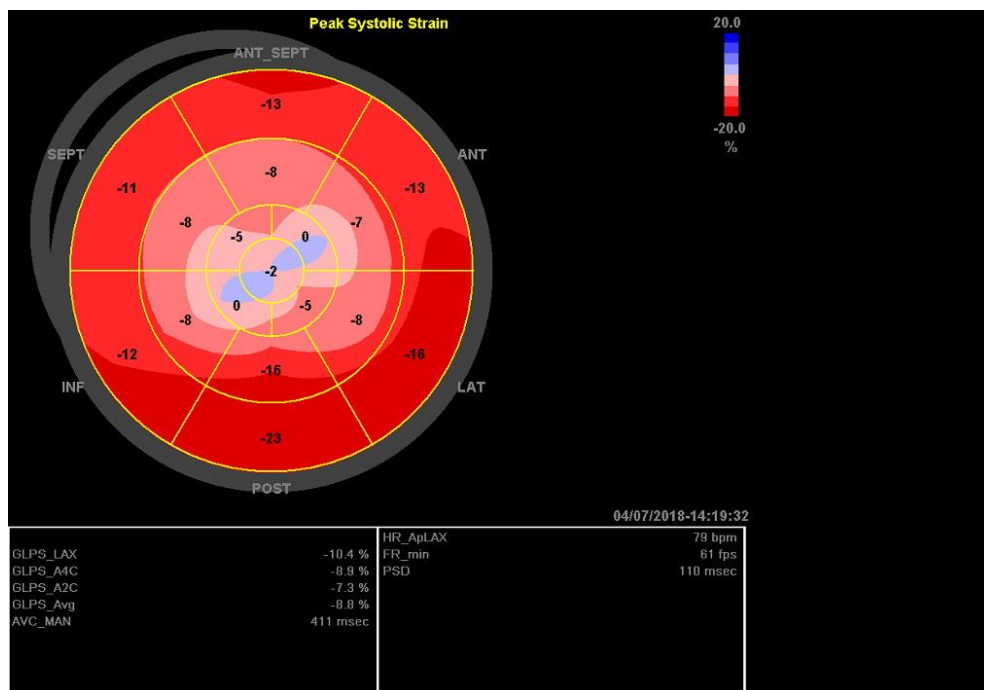
Figure 4*: Illustration of a bull`s eye plot for a typical Takotsubo cardiomyopathy (TTC) patient.*

In echocardiography, the term "strain" is used to describe regional shortening, thickening and lengthening of the myocardium. In clinics longitudinal shortening of the myocardium between the apex and base is commonly used. Myocardial strain is a principle for quantification of left ventricular (LV) function and a new tool to quantify regional differences in contraction. Positive longitudinal strain means elongation (white, blue), whereas negative strain is shortening (red). In this representation, apical segments show dyskinesia (blue color) and akinesia (white color). (90)

1.11 Stress and Takotsubo cardiomyopathy

The connection between stress and disease has been part of folk wisdom for a long time and has even made its way into our language with phrases such as "scared to death" and a "broken heart". Stressful events are common in everyday life, and because most people do not develop TTC this alone cannot explain this syndrome. Although, there are factors that can make some people more susceptible to stressful triggers. Risk factors such as hormonal processes (e.g. pheochromocytoma, stress or oestrogen depletion), endothelial dysfunction, genetic factors and a lifetime prevalence of depression have been suggested. Identified stressors are mostly emotional, such as the death of a relative or a quarrel, but can also be physical, such as the use of cocaine or subarachnoid haemorrhage. Despite the strong connection between acute stress and TTC, there is a lack of research on how patients perceive their life situation before onset of TTC and whether they have been subjected to long term stress. (91)

Recent studies suggest a predisposing influence of psychiatric disorders, psychosocial stress and personality type D (PTD) in its pathogenesis. (92) PTD is characterized by negative affectivity and social inhibition. (93) Excessive or inadequate basal activity or responsiveness of the hypothalamus-pituitary- adrenal axis (HPAA) have been suggested as sensitive indicators for health and psychological conditions. (92)

1.12 Pathophysiology of stress and catecholamine toxicity

> Stress is a physiological response that mediates the action of a stressor on its target organ. The anatomic structures that mediate stress response are found in both the central and autonomic nervous systems. Acute emotional stressors have been shown to induce brain activation, increasing bioavailability of cortisol, epinephrine, and norepinephrine. (94) The fundamental anatomic structures involved in the stress response are the neocortex, limbic system, reticular formation, brainstem, and spinal cord. (95)

When facing a threatening stimulus, and after complex neocortical and limbic integrations have occurred, the neural stress response occurs through activation of brainstem noradrenergic neurons and sympathetic adrenomedullary circuits. This results in secretion of catecholamine. (96) NE is mainly synthesized in locus coeruleus, located in the posterior area

of the rostral pons in the lateral floor of the fourth ventricle. The locus coeruleus function as a control center, and receives afferents from the hypothalamus, cingulate gyrus and amygdala, allowing emotional stressors to trigger noradrenergic responses. It contains the largest clusters of noradrenergic neurons in the brain and innervates large segments of the neuroaxis. (97) Activation of the locus coeruleus leads to increased NE secretion. This furthermore stimulates the HPAA, which consists of a complex set of three endocrine glands - the hypothalamus, the pituitary gland and the adrenal gland. The adrenal medulla synthesizes, store and release predominantly epinephrine and norepinephrine, which constitute the hormonal output of the neuroendocrine stress – response axis. (98) In addition to the locus coeruleus, the neural impulses also descend into the posterior hypothalamus, which is the pathway of sympathetic activation. Further on, sympathetic neural pathways descend through the cranial and sacral spinal cord regions and trigger the release of norepinephrine. (99) In the lateral grey column from T1 to L2-3 there are sympathetic preganglionic neurons that synapse with their postganglionic neurons. Fibers of sympathetic cardiac innervation end as sympathetic nerve terminals reaching the heart muscle and coronary circulation. These sympathetic nerve endings activate α and β postsynaptic adrenoceptors by releasing norepinephrine directly into the synaptic cleft. (100) The amount of catecholamine presented to the cardiac adrenergic receptors includes both circulating NE and EPI coupled with NE released directly from sympathetic nerve terminals. (101)

The neuroendocrine stress-response axis is crucial to maintain high levels of stress arousal for prolonged periods. (100) The neurogenic effect is cited in many studies, and an excessive catecholamine-induced sympathetic stimulation of the heart, causing an acute stunning of the myocardium, has been suggested as a pivotal mechanism in TTC. (5) Toxicity by catecholamines is assumed to be higher when released to the heart by sympathetic nerves, than reached by blood. (102)

Direct toxicity of endogenous catecholamines released into the heart via nerve terminals can cause myocardial necrosis. (103) This can result in contraction band necrosis, which histologically is one of the hallmarks for TTC. Contraction band necrosis is a unique form of myocyte injury characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response and is distinct from the polymorphonuclear inflammation seen in infarction. (104)

1.13 Role of oestrogen

Oestrogen may have a protective role on the cardiovascular system of females. It reduces the inotropic and chronotropic response to catecholamines, and thereby alters vascular reactivity. (105-107) In this way, it has an important role on the vasomotor tone through the upregulation of endothelial nitric oxide synthase activity and there is clinical evidence of oestrogen attenuating catecholamine-mediated vasoconstriction. Thereby, low oestrogen levels in postmenopausal women increase the risk of focal left ventricular wall motion abnormalities. (108) Several studies have demonstrated that myocardial β – adrenoceptor mediated positive inotropic responses are greater in male hearts than in age – matched female hearts, and that these differences are mediated by reduced β-1 adrenoceptor signalling in women. Reduced myocardial β-1 adrenoceptor signalling in ovulating women seems to be protective against myocardial insults, including stress – induced catecholamine production and ischaemia – reperfusion injury. (109, 110)

Ovariectomized rats with oestrogen supplement lower the negative effect of immobilization and stress on left ventricular systolic function, thereby protect the myocardium from catecholamines thorough activation of some specific pathways. (111, 112)

1.14 Role of endothelial dysfunction

Data from large cohorts have recently shown that the prevalence of cardiovascular risk factors such as hypertension, hypercholesterolemia and smoking in TTC patients are significant. (19, 113, 114) Additionally, evidence show that most cases occur in patients with comorbidities such as neurologic and psychiatric disease. (113) These are associated with endothelial dysfunction and might therefore constitute a previously unrecognized predisposing factor for this syndrome. (115) The endothelial dysfunction can also be a part of the explanation to why TTC is more common in postmenopausal women. It is recognized that these women have both age – related and oestrogen- deficiency – related coronary vasomotor abnormalities. (116-118) Under physiological circumstances, oestrogen beneficially affects the coronary microcirculation through endothelium – dependent and –independent mechanisms, thus improving coronary blood flow. (117)

1.15 Clinical presentation

Debut symptoms often include chest pain and/or dyspnea, which have been reported in 70% of patients. Additionally, ECG abnormalities with ST-segment elevation, usually in precordial leads and cardiac biomarkers with limited changes. Symptoms, clinical signs, and electrocardiographic findings in patients with TTC are suggestive of an ACS (acute coronary syndrome). (17) Observations of syncope, cardiogenic shock and ventricular fibrillation are also seen, presented in early onset. (11, 23, 27, 28, 30, 52, 119) Other symptoms seen more seldom are nausea, weakness and vomiting. (34, 120) When comparing genders, it is noticed that chest pain is reported more frequently in women, while dyspnea, syncope and no or other symptoms occurred with similar frequency in both sexes. (16, 29, 39)

Reciprocal ST-segment changes and abnormal Q waves are often absent in TTC. (54) Patients with TTC and ACS share the same cardiovascular risk factors, but angiographic findings show that coronary atheroma and plaque rupture do not explain the pathophysiology of TTC. (62) To distinguish TTC from an ACS based on the ECG alone, is challenging and therefore access to emergency coronary angiography should be the procedure in all acute patients resembling ACS. (17)

1.16 Clinical management

Management of patients with TTC is overall supportive and conservative. Left ventricular depression is treated with diuretics, beta - blockers and angiotensin converting enzyme inhibitors. Additionally, beta - blockers may block catecholamine excess and have an essential role in reducing LVOTO by decreasing basal segment hypercontractility. (15) TTC carry a considerable morbidity and mortality risk when untreated.

Most of TTC cases can be managed with follow up only, but the long-term prognosis is not entirely positive with major adverse cardiac- and cerebrovascular event rate of 9, 9% per patient year. (29) In the acute phase, left ventricular ejection fraction (LVEF) is often severely reduced, far more than for example after an acute myocardial infarction. Therefore, approximately 50%, of all TTC patients suffer from pulmonary congestion, and as much as 10-20%, from acute pulmonary oedema. (29, 121) Further on, formation of ventricular

thrombi may complicate the clinical course. Anticoagulants for primary prevention can be useful, also if the LVEF is relatively reduced. (121) No specific long-term pharmacological treatment for TTC has been established so far, only complications are treated. In a review form 2017 published in the "International journal of Cardiology", Efferth et al. highlighted that there are no consensus recommendations for long – term management of TTC to prevent recurrence. (122) They referred to a multicentre retrospective study which found that chronic treatment with beta – blockers, ACE – inhibitors, calcium channel – blockers and aspirin did not improve left ventricular function. (123)

1.17   Recurrence

The five-year recurrence rate is 5-22% after initial TTC have been reported, with the second episode occurring 3 months to 10 years after the first. (34) Most studies have reported no difference in recurrence between genders, but some studies have found that the predominance in women is maintained. (16, 29) Hormone replacement therapy does not exclude the risk of developing TTC, (124) and no evidence supports any specific treatment to prevent recurrence. (125)

1.18   Prognosis

Recent studies have reported life-threatening complications including left ventricular free wall rupture, LVOTO, thrombosis and cardiogenic shock, and the in-hospital or long-term outcomes are not necessarily as benign as previously reported. (126) In- hospital mortality was observed in 2-5% off TTC patients. (34) During hospitalization, non – life threatening complications occur in a high proportion (20-53%) of both female and male patients. (16, 29, 39)

1.19   Psychiatric disorders

Anxiety and depression have been shown to increase the incidence of cardiovascular disease, cardiovascular events, and death. In one of the few publications, anxiety as a trait was prominent in 60% of TTC cases. (127) High occurrence of these diseases is associated with

increased catecholamine levels and may characterize individuals susceptible to TTC. Until 2016 it was only two prior studies which addressed the possible association of anxiety or depression with TTC; they have showed conflicting results. (93) Recent retrospective studies have suggested that premorbid psychiatric disease could be an important predisposing risk factor for TTC. This finding suggests an influence of psychological factors on TTC incidence. (128)

1.20 Personality traits and cardiovascular disease

It is suggested that some individuals are particularly vulnerable to psychological distress, which can lead to the syndrome. Developing TTC relies on responses to distressing factors and cardiovascular reactivity to emotional stress, which is dependent on individual differences in personality traits. These individual differences affect the pathophysiological mechanisms that result in TTC. (93, 129) It is important to remember that the pathogenesis of cardiac disease depends not only on the number and severity of stressors, but also on unfavorable stress – management strategies such as negative cognitive appraisal and external locus of control. (130)

Comprehensive assessments on psychological measures of stress in patients with TTC, have been obtained in few studies. Adverse psychological factors are suggested associated with TTC, which may persist well after the acute episode. (4) Characteristic thoughts, feelings and behavioral patterns among the patients will enhance understanding for triggers that make them vulnerable to TTC development. (93) One personality type that may be particularly relevant is PTD. (131) Some researchers like Compare et al. (2013) claim that it has been established as an independent predictor of acute cardiac adverse event. (93) An important addition in the process of clinical diagnosis and decision-making is life events, individual psychology (vulnerability or resilience), social factors (living conditions) and stability of social relations. (122)

1.21   Aim of the thesis

The aim of the study was to assess if the personality trait of neuroticism, can increase the vulnerability for Takotsubo cardiomyopathy. Many studies have related takotsubo to psychological stress, but is the personality even more crucial?

2   Material and method

2.1   Management

A literature review was conducted. We used all MeSH – terms for Takotsubo cardiomyopathy, personality type D, anxiety disorders, and psychological stress from PubMed to find appropriate publications and literature in MEDLINE, in august 2018. The MeSH-terms were limited with title, abstract and keyword. Since personality traits and neuroticism are defined concepts and not MeSH terms in PubMed, we made a separate search in MEDLINE with limitations title, abstract and keyword. Additionally, "exploded" the term personality, takotsubo cardiomyopathy, anxiety disorders, and stress psychological in MEDLINE and included the search results. Our search was limited to literature in the time period 2007-2018. Some review articles published during these years contained original articles released prior to 2007. Due to their relevance and important contribution to purpose of this study, they were included in our thesis. Study designs were limited to clinical studies, comparative studies, interviews, journal articles, randomized control trials, "reviews" and systematic reviews.

When we read through the articles from the final search, we came across relevant content from other studies and thereby included these references as additional literature.

We searched separately for "Consensus of takotsubo cardiomyopathy mayo criteria" in PubMed. This was performed past our literature search to find the latest update regarding diagnostic criteria for TTC.

2.2   Modified PRISMA


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┌─────────────────────────────────┐
│ Records identified through      │
│ database searching              │
│ (n=208)                         │
└─────────────────────────────────┘
                 │
                 ▼
┌──────────────────────┐   ┌─────────────────────────────────┐
│ Records excluded     │◄──│ Abstract and conclusion screened│
│ after reading the    │   │ (n=208)                         │
│ abstract or no       │   └─────────────────────────────────┘
│ abstract available.  │                │
│ (n=120)              │                ▼
└──────────────────────┘   ┌─────────────────────────────────┐
┌──────────────────────┐   │ Full-text articles assesed for  │
│ Full-text records    │◄──│ eligibilty (n=88)               │
│ excluded due to      │   └─────────────────────────────────┘
│ irrelevance (n=49)   │                │
└──────────────────────┘                ▼
                          ┌──────────────────┐   ┌──────────────────┐
                          │ Articles included│◄──│ Additional records│
                          │ in results (n=40)│   │ included in       │
                          └──────────────────┘   │ results(n =1)     │
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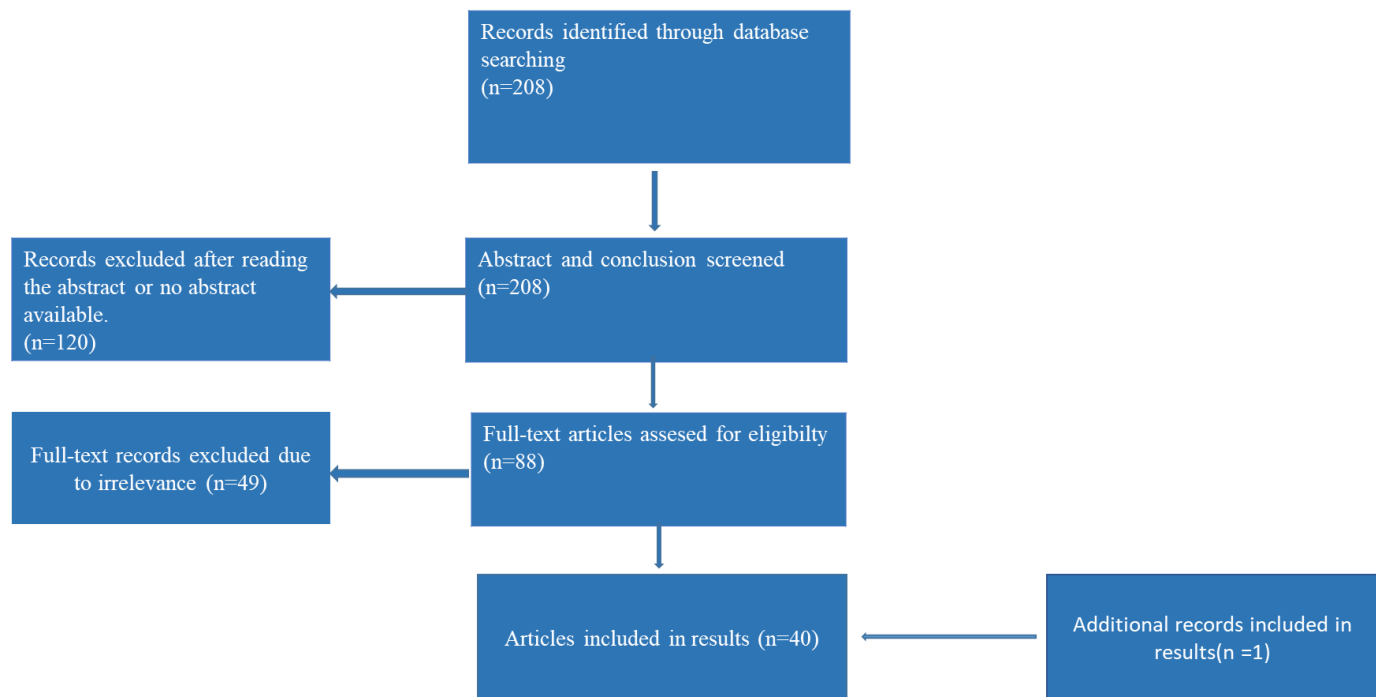
Figure 5: *Modified PRISMA diagram showing a summary of the literature search and selection of articles.*

3   Main results

Our literature findings include different levels of documentation. We present the results accordingly; case reports and original articles. Since reviews are based on original articles, they are presented under the same subheading. The intention of presenting results in this order is to get a comprehensive overview of the literary hierarchy.

Although the case reports are not scientifically significant, they were included in our results to see if the individual cases correlate with the findings in the overall literature regarding TTC.

3.1   Case reports

The reports ranges from 2008 – 2018. 2 of 22 were excluded due to irrelevance. We included specific themes which were encountered through all case reports.

3.1.1 Gender and age

Two men were reported, remaining were women. Age range was 43-86 years, except for one woman whom was 23 years old. Majority of women were postmenopausal.

3.1.2 Triggering events and catecholamines

Different triggering factors were disclosed. Most of them emotional, some with a physical factor and few related to medical illness alone. Considering emotional cases, concerning our thesis, family drama (quarrel, separation, infidelity) and loss of a family member/spouse is worth mentioning. Still, no vulnerability for the development of TTC has been scientifically proven. In 5 of 20 cases, physical stress was categorized as the main reason for TTC. In the remaining 15 published reports, a triggering factor was thought to be emotional stress, or both, emotional and physical stress. One case-report described positive stress triggering TTC. This applied to a woman receiving a lifetime teaching award.

Regarding explanation of pathophysiology, 9 of 20 reports highlights catecholamines as the main reason for TTC, while 11 reports do not focus on any pathophysiology behind the syndrome.

3.1.3 Clinic

Time from onset of symptoms to first medical contact was from 30 minutes to 9 days. The most prominent symptoms were chest pain and dyspnea, reported in 17 of the 22 patients. Among the remaining 5 patients, 2 patients developed TTC during anesthesia or operation, thereby no onset symptom could be reported. 3 patients acquired it as a complication to another medical emergency. Presenting symptoms here were also dyspnea and chest pain. Overall, patients showed ECG changes consisting of ST – segment elevation and T – wave inversions, with little variation in presentation. Only one patient had a normal ECG. Further on, slightly elevated Troponin T or I, reduced EF 20-56% and hypokinesis or akinesia of the mid – or apical part of the left ventricle. 2 of the 22 patients showed an atypical pattern on echocardiography: 1 with dyskinesis of mid- septal, anterior and inferior wall segment and hyperkinetic function of basal and apical segments, and the second with mid – ventricular akinesia with preserved basal and apical wall motion. Coronary angiography demonstrated

normal coronary vessels in 20 patients. 1 patient had total occlusion, and another had some plaque changes in the coronary vessels.

3.1.4   Treatment and comorbidity

Congestive heart failure treatment with diuretics, B-blocker, anticoagulant, ACE-inhibitors, were given after the diagnosis of TTC was confirmed. Additionally, relevant medications for comorbidity. 12 of 22 patients had hypertension, 5 of them with additional hyperlipidaemia. 6 of 22 had several diseases and 9 of 22 had no earlier cardiovascular disease. 3 of the 22 patients had earlier psychiatric history. In one of the reports a patient had three recurrent episodes, before the psychiatric history was examined. (132) 3 articles mentioned neither medical nor psychiatric history.

3.1.5   Recurrences and deaths

3 of 22 patients had recurrent TTC. A 43-year-old woman had 3 recurrent episodes within 4 months. Another 51-year-old woman had 3 TTC episodes during 4 years. The last one, an 83-year-old woman had 1 episode of recurrence, both episodes due to mild physical stress, with 4 years apart.

3.1.6   Prognosis

Only 1 patient died. This patient was also the youngest patient, a 23-year-old woman. Her death was described as cardiac arrest due to life – threatening ventricular arrhythmias caused by TTC. All remaining patients had normalized ECG and cardiac parameters within 6 months.

3.1.7   Evolution of TTC diagnostics

Regarding criteria for diagnosis, 14 of 20 reports do not mention Mayo criteria nor other criteria which they have based their diagnosis upon. With this in mind, we acknowledge the importance of well-defined criteria for diagnosis of TTC. This problem is addressed in one

case report from 2018, which claims that there is no single diagnostic definition for TTC. (133)

We could detect a clear change in the way of viewing the diagnostic criteria of TTC. From 2015 and onward, some reports are questioning the absence of coronary obstruction in the diagnosis of TTC. (64, 133, 134)

> When the presence of significant coronary artery stenosis (>50%) does not supply the area and extension of the myocardial dysfunction, it should not be considered an exclusion criterion for TTC. The coronary artery disease (CAD) is unlikely to be the cause of the myocardial stunning that characterizes TTC and can be considered only an "innocent" bystander. (64)

3.2 Original articles

We obtained original articles in two ways. Firstly, as independent publications and secondly as a part of reviews. Out of 28 independent original articles 14 were excluded due to irrelevance. Out of 37 reviews, 6 were included. We only present findings in reviews which were not previously acknowledged from original articles. Several of the independent articles reoccurred in our reviews.
Specific themes which were encountered through all case reports were included.

3.2.1 Gender and age
We will provide some examples to show that, despite varying sample size in studies, there is a predominance of postmenopausal women.

Kurisu et al. (2010) analyzed the presentation of TTC in both genders. Among their 102 patients, 13 were male and 89 females. No significant difference in age, body weight, hypertension or diabetes was observed, except for height. Neither any significant difference in ECG was noticed. The high incidence of in-hospital onset of TTC in male patients, was cited to physical stress. Thereby, it is suggested that physical stress is more influential for TTC development in men. Study done by Rouzaud et al. (2013) involved 14 patients where 12

were women. Delmas et al. (2013) included 45 patients, with 43 females of whom 41 were postmenopausal. (128, 135, 136)

3.2.2 Psychiatric disorders and personality traits

An article by Scantlebury et al. (2016) is the only publication we have managed to find which have neuroticism linked to TTC as a part of their research issue. The focus of the study was on the neuroticism domain. Regarding personality, the FFM (Five Factor Model) divides personality into five major domains (also called factors). These are neuroticism, extraversion, openness, agreeableness and conscientiousness. Neuroticism can further be divided into facets. The six facets of the Neuroticism scale are: Anxiety (prone to worry, fearful, apprehensive), Angry hostility (tendency to experience anger and related states such as frustration and bitterness), Depression (prone to feelings of guilt, sadness, and loneliness), Self – consciousness (sensitive to ridicule, prone to feelings of inferiority), Impulsiveness (inability to control cravings and urges), and Vulnerability (difficulty coping with stress). (137)

Scantlebury et al. hypothesized that patients with TTC would have elevated levels of neuroticism (tendency to experience negative affect) and greater vulnerability to stress. Their research included 53 participant which had experienced TTC, predominantly consisting of women and with mean age 71,1 ± 10,3 years. (137)

However, their results showed that TTC patients demonstrated no difference in neuroticism compared with the normal population. (137) They also found that TTC patients with emotional triggering showed no difference on the Neuroticism factor when compared with those without emotional triggering. There were 3 patients in the study with recurrent TTC which had higher Neuroticism scores, but this was not statistically significant. (137)

Additionally, vulnerability to stress, as measured on the Vulnerability scale, was similar to the general population. None of the Neuroticism facets scores were statistically different from the normative sample. (137) These results corroborate with findings by Waldenborg et al. (2011) They performed a systematic screening by psychiatric interview and did not find abnormal prevalence of major depressive disorders in patients with TTC. (138)

These findings are in contrast to a study by Delmas et al. (2013) demonstrating that TTC patients have higher rates of anxiety-and depression diagnoses (128), as both diagnoses are correlated with elevated levels of neuroticism. Delmas et al. used MINI (mini international neuropsychiatric interview) for psychiatric assessment, focusing on prevalence of major psychiatric diseases and chronic psychological stress (CPS). Two groups were compared, 45 cases with TTC and 50 controls with ACS. This was the first study to draw a line between the psychological background of TTC patients and anxio-depressive disorders (ADD). CPS was defined by the presence of personal, familial or social difficulties reported by the patients (e.g. dependent child or husband, recurrent conflicts and many deaths in relatives). Acute triggers seen in the study were funeral, bad memories, disappointments and separation. (128)

In 78% of patients an acute stressful event before onset of TTC was identified vs 18% in ACS patients. Triggering stress was emotional for 56% of patients with TTC and 16% for ACS patients, which was significant. Besides the acute stress, chronic stress was found in 44% of TTC patients and in 18% for the ACS group. 78% of TTC patients had ADD vs 26% in the ACS group. Hereby, Delmas et al. confirms that major depressive disorder and generalized anxiety disorder are common in patients with TTC and more frequent than in those with ACS. This was earlier presented by Del Pace et al. (2011). They found that high – anxiety trait was common in patients with TTC (60%). Although, here it was no difference compared to STEMI patients (52%). (127)

Compare et al. (2013) researched on whether PTD can be identified in TTC patients. Their study was based on 111 patients. There was 74 TTC cases: 37 patients had TTC due to an emotional trigger and 37 patients with TTC due a physical trigger. The control group consisted of 37 patients with AMI with an emotional trigger. There were predominantly women in all groups, with mean age 66 years old. In their research they found that patients who developed TTC with an emotional trigger had a higher proportion of PTD 3 months after the acute presentation. Subsequently, it was reported that persistence of negative psychological impact of the episode of TTC lasted up to 1 year. In comparison with those without emotional triggering. Of the 37 TTC patients with emotional triggers, 28 (76%) were categorized as type D compared with 13 (43%) TTC patients without emotional triggers and 12 (32%) AMI patients. The differences were significant. (93)

In 2014, Compare et al. did another study where they examined the wellbeing 1 year after the acute event of TTC. 37 TTC patient were matched with 37 AMI patients. Age range was from 50 – 62 years, and the study consisted predominantly of women. All patients were assessed for health-related quality of life (HRQL) and psychological distress at baseline and 1 year later. They did this by investigating HRQL, and emotional burden subsequent to cardiac events in TTC patients. (139) HRQL was assessed by using the MacNew Heart disease Health – related Quality of Life self-report questionnaire, while psychological distress was assessed using the Psychological General Well-being index (PGWBI). (139)

The results showed that PGWBI global, PGWBI depressed mood, PGWBI vitality and MacNew (measuring HRQL) global decreased significantly in both groups. Additionally, the percentage of patients with a moderate or severe rating of psychological distress 1 year after the cardiac event, was significantly higher in the TTC (70,2%) group. This compared with AMI (37,8%), independent of trigger event topology (emotional vs. physical). Findings were shown to be independent of gender. (139)

In 2015, the international Takotsubo registry revealed that more than half of patients with TTC had preceding neurologic or psychiatric disorders. (29) Among the psychiatric disorders related to TTC, anxiety is one of the most frequent. (140) Similar to Del Pace et al. research in 2011, Lazzeroni et al. did a recent study (2018), investigating if there was a link between TTC and anxiety. The study was retrospective and anxiety disorders were evaluated from medical records, pre – existing psychiatric diagnosis and/ or chronic use of benzodiazepines. 56 TTC patients were included in the study, mean age was 70 years, and women were overrepresented. Patients were divided into TTC with exclusively emotional trigger, TTC with a physical trigger and TTC with an undetermined trigger. (141)

Their results showed that 31 of the 56 TTC patients had a pre – existing anxiety disorder. Additionally, they found that exclusively emotional stressful events were more common in TTC patients with pre – existing anxiety disorder. In contrast, undetermined stressful events were more common for TTC patients without a history of anxiety disorders. (141)

In 2016 Goh et al. also explored the themes anxiety and depression in TTC patients. Their psychiatric assessment was through HADS (hospital anxiety and depression scale), which is designed to detect depression and anxiety. Their results substantiated Del Pace et al. (2011)

Depression was not associated with TTC and neither conditions were seen frequent in ACS patients. Summarizing with higher levels of anxiety are associated with particularly emotionally triggered TTC. (127, 142)

Another study that supports the assertions that anxiety is a precipitating factor for TTC, was a study by Smeijers et al. in 2016. They examined whether patients with TTC had higher levels of psychological distress (depressive symptoms, perceived stress, general anxiety), illness – related anxiety and distinct personality factors. This compared with healthy controls and patients with chronic heart failure. TTC patients were identified by reviewing electronic medical records over a 5-year period (2009 - 2014). The study consisted of 18 TTC patients, 19 healthy controls and 19 patients with chronic heart failure. Patients with TTC in response to surgery or acute injury were not included. The distribution of women vs. men were relatively similar in all 3 groups, with age ranging from approximately 50 – 80 years. Psychological measures were obtained 23 ± 18 months past the acute event of TTC. NEO – FFI (NEO Five – factory Inventory) were used to assess personality factors, depressive symptoms were assessed using Patient Health Questionnaire (PHQ-9) and the DS – 14 for PTD. (4)

Results showed that TTC patients did not display significantly elevated levels of perceived stress or general anxiety. However, measurement of depressive symptoms and illness – related anxiety were significantly higher in TTC patients compared with healthy controls. Regarding PTD, the subscales negative affectivity and social inhibition did not differ between TTC patients and the control groups. (4)

3.2.3 Impact of long-term stress

As opposed to the studies mentioned above, focusing on acute events prior to TTC, we now present the impact of long-term stress. Wallström et al. (2016) did a qualitative study presenting personal experiences from the informants. Data were collected through narrative interviews with aim to analyze impact of prolonged stress. Their findings based on low intensity stress experienced over a long time period triggering TTC, rather than an acute stressful event. Situations could be addressed back years, even decades. Another dominating feature were their exaggerated worrying nature regarding circumstances. Informants did not

seem at peace with their situation in life or how it had become. Main concerning themes were everlasting responsibilities, recurring injustice and perpetual uncertainty. Conclusively their findings indicate that prolonged stressful circumstances make individuals vulnerable. This vulnerability further on cause increased risk for onset of TTC. They claim that this study might be an answer to why a minority of people develop TTC, although a lot more are exposed to stress during their life. (91)

Further on in 2017, Rosman et al. explored the cumulative impact of stressful life events on the development of TTC. They sought to examine the association between type, timing and number of stressful life events. This study was based exclusively on women. Included in the study were 45 TTC patients, 32 myocardial infarction (MI) patients and 30 healthy controls (HC). Medical history, including history of anxiety and depression was obtained from medical records. Results showed that onset of TTC was associated with exposure to multiple stressful life events during 6 months prior to index hospitalization, but not associated with exposure to an acute, recent event. The mean total number of stressful life events differed significantly between groups, with TTC women reporting a greater number of prior stressful life events than the control groups. A history of anxiety disorders was also more prevalent among TTC cases than control groups. (143)

3.2.4 Positive emotional stress

A publication by Ghadri et al. (2016), is the only original article in our research which explored the role of positive emotional stress. Their results show that out of 485 TTC patients, 4.1% experienced positive emotional stress, while the remaining 95.9% experienced negative emotional stress. Women were overrepresented in both groups. Of note, the majority of patients was unemployed or retired at the onset time. Positive factors were birthday party, wedding, family party or winning jackpots on casino. This study may indicate that both happy and sad life events, may share common pathway in CNS. Regardless of the triggering stress cause, it is how an individual process and react to it that can trigger TTC. (6)

3.2.5 Pathophysiology of stress

Due to lack of relevant literature, results from one study is presented for this topic.

Smeijers et al. (2015) presented the hormonal responses to different kind of stress in 18 TTC patients. Stress was categorized as: physical exercise, mental challenging task and emotional recall of anger, irritability and distress. They were compared to 19 patients with heart failure and 19 healthy controls. Participants rated mood adjectives on a 7 – point Likert scale. Hormones analyzed were dopamine (DA), NE, EPI, adrenocorticotropic hormone (ACTH) and cortisol, and were compared to baseline levels. Levels of DA and NE during mental stress and exercise were significantly higher in patients with TTC compared with healthy controls. No differences were observed for EPI levels during mental stress. Elevated levels of cortisol and ACTH were also seen, but not differing in groups. Responses of the HPAA and hemodynamic reactivity were not increased in TTC patients. Another point worth mentioning is that emotional response to mental stress were not exaggerated in TTC but showed a blunted arousal response compared with healthy controls. Their conclusion provided preliminary evidence of hyperreactivity of the sympathetic nervous system. This in response to mental stress and exercise, but no emotional hyperreactivity in patients with TTC were observed. Their findings also corresponded with literature on acutely elevated catecholamine levels during TTC admission. The lower stress-induced arousal response in TTC versus controls was unanticipated considering studies exploring psychological traits related to TTC. (92)

We now continue to present original articles obtained from reviews.

3.2.6 Psychiatric disorders and personality traits

A patient cohort that may be predisposed to development of TTC is the population with psychiatric disorders. (144) Summers et al. (2010) reports a higher prevalence of mood disorders and anxiety in TTC patients. They found that 68% of patients had either anxiety or depression, and prevalence of those two diseases were more frequent than in those with myocardial infarction. Furthermore, in retrospective analyses, these patients were more likely to be divorced, to be living alone, and to have a family history of affective disorders. (145) Not only may psychiatric disorders predispose to TTC, but an exacerbation of psychiatric illness may also acutely trigger TTC. (146)

Redfors et al. (2013) reports in their review that acute severe emotional stress can trigger TTC and thereby is given the name stress induced cardiomyopathy / broken heart syndrome. They sum up studies which have found that anxiety and chronic stress both are associated with higher odds for developing TTC. Further on they believe that TTC may occur acutely in biologically predisposed individuals, this in response to an acute stressor. This predisposition is thought to be caused by chronic stress or impaired well-being. (146)

Lacey et al. assessed psychosocial risk factors such as depression, anxiety, trauma, extraversion, and neuroticism in different cohorts. Two groups had experienced an earthquake: a TTC groups who experienced initial symptoms immediately after the earthquake, and healthy controls experiencing the earthquake. The last groups of patients had TTC but were not affected by the earthquake. Psychiatric symptoms and personality traits showed no difference between groups. However, 59% of patients with earthquake – triggered TTC and 42% with sporadic TTC had experienced trauma in the past. They also found that both TTC groups had a more pronounced expression of neuroticism. (147)

3.2.7 Pathophysiology of stress

Balkin et al. (2011) report in their summary a multifactorial pathogenesis in patients who develop TTC. A pattern is described starting with; 1) extreme unrelenting emotional event which unleashes a catecholamine surge as a result of positive feedback loop in the psychologic stress system 2) extra ordinarily high levels of catecholamines disrupt cardiac function through direct cardiomyocyte toxicity, 3) excessive coronary artery adrenergic stimulate and the postmenopausal oestrogen-deficient women is particularly susceptible to the actions of the catecholamines surge. (148)

Evidence supporting this mechanism were provided by Wittstein et al. (2005) in their research on catecholamine levels after sudden emotional stress, comparing TTC patients with AMI patients. (31)

Results showed that TTC patients demonstrated both higher plasma EPI levels as well as NE levels in comparison to the AMI group, after sudden emotional stress. Initial plasma levels were several times those of patients with myocardial infarction and remained markedly elevated even a week after the onset of symptoms. (31)

In clinical states of catecholamine excess, contraction-band necrosis has been described. This form of necrosis has also been observed post mortem in people who died under terrifying circumstances, such as fatal asthma (149) , and violent assault (150), suggesting that catecholamines may be an important link between emotional stress and cardiac injury.

Dysregulation of the HPAA can be influenced by chronic stress and contribute to the development of cardiovascular disorders. (130) It has been formerly shown that vagal tone decreases while the response to adrenal medullary hormone increases, when patients with depression experiences stressful events. (144) Additionally, some patients with depression have shown very high amounts of NE release, which can lead to higher levels of circulating catecholamines. (151) Depressed patients showed an exaggerated NE response to emotional stress. (152) Some reports claim decreased catecholamine reuptake due to impairment of the NE- transporter in some patients with panic disorder and anxiety. This may lead to prolonged stress response. (153)

Other studies have sought to examine the role of cortisol in patients with TTC. In some studies, it has previously been suspected that the cortisol level in TTC patients would differ from healthy controls. Kastaun et al. reports in their own investigation that no difference has been detected. (154) This applies to serum concentrations of evening cortisol, basal urinary concentrations of cortisol and basal morning salivary cortisol. (155, 156) The result was supported by Collste et al, which found no difference in morning salivary cortisol levels between patients with TTC and healthy controls. (155) On the other hand, cortisol levels during mental stress is unclear. Collste et al. and Kastaun et al. both found that the cortisol stress response (CSR) was reduced in TTC patients compared to healthy controls. Nevertheless, both emphasize that this result is inconclusive due to unclear protocol and small sample sizes. (154, 155) Despite a blunted cortisol response, patients with TTC felt more nervous during the stress experiment. (154)

4 Discussion

One of the challenges with literature regarding TTC and psychosocial risk factors is the paucity of data. Additionally, large cohorts and studies for extended periods are missing. Small sample sizes apply to most studies and may be the most significant limitation in terms of findings within this field.

Anxiety and depression are traits observed in TTC patients. Studies report a link between anxiety and TTC (127), while the correlation between depression and TTC is uncertain. Although, depressed people show an exaggerated response to emotional stress. (151) It is still difficult to determine whether emotional stress results in anxiety, anxiety contributes to TTC or TTC itself arises anxiety. (142)

> It is important to recognize the difference between anxiety as a "trait" versus anxiety as a "state". In the field of personality assessment, traits are conceptualized as stable personality dispositions that are relatively invariant across situations, and that have a significant biological substrate. Conversely, *states* are transient emotional reactions that are highly sensitive to the situational context. (137)

In the study by Del Pace and colleagues (2011), patients were studied during the index hospitalization, and in the study by Compare and colleagues (2014), evaluation was done at 3 months following TTC. In these cases, findings may be reflective of ongoing life stressors that were associated with the index event (a "state") rather than an intrinsic personality trait. (127, 137, 139)

Neuroticism and PTD are both characterized by negative emotional states. So far, no connection is observed between PTD, neuroticism and TTC. Enough research has not been done.

TTC is perceived as a female disease. This with good grounds, as most patients are postmenopausal women. One theory regarding postmenopausal women and their vulnerability for TTC is changes of oestrogen levels. In sufficient levels, oestrogen has a cardioprotective role. While low levels of oestrogen may make the heart more vulnerable for the catecholamine surge in TTC.

In regard to criteria for TTC diagnosis, there is currently a lack of international unity. An expert consensus statement was presented by Ghadri et al. in 2018. (157) This paper addresses the importance of universal agreement regarding guidelines for TTC. Diagnostic criteria have been presented several times earlier. The first criteria were proposed by Abe et al. in 2003. (20) A year later (2004), a dedicated group of cardiologists from the Mayo Clinic proposed new criteria's. (41) Since then other research groups have come up with several proposals, with variation according to which country the criteria have been proposed by. (157) The consensus paper from 2018 submitted new international diagnostic criteria, the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria). As some of the formerly exclusion criterions are a part of the new guidelines, the paper presents a justification for why they should be included. According to InterTAK Diagnostic criteria, pheochromocytoma is not an exclusion for TTC diagnosis, since it may serve as a trigger. (157) In addition, TTC may coexist with ACS (158), and it has been reported that ACS itself can trigger TTC. (159-162) One should suspect coexistence with TTC and obstructive coronary disease when the area of wall motion abnormality is not supplied by the obstructed vessel. (163) Due to this, significant coronary artery disease is not a contradiction in TTC. (157)

"While the evidence supports a link between acute psychological triggers and cardiovascular risk, there is no convincing evidence for specific prevention at an individual level." (164)

Limitations

We have highlighted a specific aspect of TTC, and thereby relevant literature are limited. Additionally, material obtained was based on small populations, which may influence our results. It is thereby difficult to claim that our results are significant. In addition, many articles which was appropriate for this thesis, were not accessible through University of Tromsø`s online access to MEDLINE.

Strengths

To analyze a subject with limited relevant literature is also a strength, because it raises interest towards a new aspect.

Implication

So far, our study may not contribute to any change in clinical practice. Nevertheless, it can contribute to raise awareness regarding TTC and neuroticism at this point. Ultimately, and most importantly, this issue needs more research to ensure a better understanding of the risk factors for TTC.

5   Conclusion

Throughout life, people will experience different stressors, with various degree of burden. Response to distressing factors build upon the way individuals process and react to it, along with cardiovascular vulnerability. This in turn depends on personality traits, vulnerability and resilience. Our results have shown an increased prevalence of psychiatric disorders in TTC, and anxiety has proven to be a prominent feature. However, there are no unambiguously results regarding the correlation between TTC, depression, PTD and neuroticism.
Most studies identify stressful events immediately preceding the presentation of symptoms. However, some results indicate that exposure to repeated stressful events, rather than temporal proximity, may have a more decisive role in onset of TTC.

In most studies TTC patients are compared with AMI patients, because they have similar clinical presentations and are expected to have a high sympathetic tone.

Throughout it is evident that more postmenopausal women are reported compared to men and younger adults. Majority have an emotional stressor combined with physical or isolated emotional stressor. Presenting symptoms are chest pain and dyspnea.

Regarding aim of the study, evidence is inconclusive at this point. Few articles on neuroticism as a precursor to TTC are published, and sufficient knowledge is not available. Several and larger studies are still needed. Therefore, we have attempted to draw attention towards this topic, through our thesis.

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List of figures

Summary of grade

Reference:		Design: Case-Control study	
Kastaun S, Schwarz NP, Juenemann M, Yeniguen M, Nef HM, Moellmann H, et al. Cortisol awakening and stress response, personality and psychiatric profiles in patients with takotsubo cardiomyopathy. Heart. 2014;100(22):1786-92.		Documentation	2
		GRADE	Low

Purpose	Materials and Methods	Results	Discussion and Comments
To identify predisposing psychiatric and personality pattern, as well as stressful life events, that may be linked to altered cortisol profiles in patients with TTC compared to NSTEMI patients and healthy controls.	*Sampling*: 19 female TTC patients (Case) were compared with 20 female NSTEMI patients (controls) and with 20 healthy women (Control). Healthy women were recruited via announcements from community facilities, voluntarily. Inclusion criteria were in line with the Mayo Clinic criteria for cases, whom were recruited from Kerckhoff Heart and Thorax Center. Uncertain how the NSTEMI were recruited. All gave written, informed consent. The groups were matched by age (mean age 60.5±9.2), and the TTC and NSTEMI patients were additionally matched by their index event date in relation to study inclusion (mean months 18.4±8.5) The most prominent Pharmaceuticals (if used by more than two patients) that are known to influence the physiological stress response was recorded as well. None of our participants took oral contraceptives or corticoids *Data collection*: Saliva cortisol, its concentrations are closely correlated to serum cortisol. Salivette sampling device were used. Samples were centrifuged at 3500 rpm for 5 min and frozen at −20°C until assayed. An ELISA determined free cortisol concentrations. Catecholamines: was refrained from measurements, because saliva is a poor index to measure acute changes in the sympathetic activity, and venipuncture itself can lead to activation of stress systems.	- At acute hospital admission, TTC patients had a significantly lower left ventricular EF than NSTEMI patients. ((MD diff)=−20.0 95% CIs −25.0 to 10.0) - Compared to the NSTEMI patients, TTC patients underwent significantly more often an acute stressful trigger prior to their heart attack. That trigger was frequently a severe familial or professional argument. - The life-event inventory shows that TTC patients experienced spousal loss and severe, recurrent familial or professional arguments more frequently than the controls. More traumatic life events (domestic abuse, forced abortion, car accident with severe injury and spousal loss) happened to TTC patients when compared with NSTEMI patients and controls. - TTC patients more often reported domestic abuse as their predominant motivation for therapy than the NSTEMI patients or controls did.	-Were the case-control groups recruited from comparable study populations? No, the selection of the population was not comparable, due to lack of background information. -Is the case group's condition sufficiently described/validated by diagnoses? YES -Does the control group have the current disease? NO. -Have the authors considered important confounding factors in the analysis? Unclear, some factors are highlighted and others are not mentioned.
Conclusion	Laboratory stress experiment: The participants received introductions to study protocols, which spared details about the 'stress experiment', and were asked to provide their first salivary sample on the afternoon prior to the lab session. They were advised not to eat, drink (except non-carbonated water), or smoke 2 h prior to the samplings. Individual examinations were performed between specific time. To reduce initial excitement, all participants listened to relaxation exercises for 15 min. The 15 min stress induction phase followed, always conducted by the same psychologist. Saliva was collected at 15 min intervals: at arrival, after relaxation, after stress and over the following 45 min while the subjects had to fill out the psychometric questionnaires. Heart rates and nervousness were measured simultaneously.	*Personality traits, psychiatric status and chronic stress* Group differences in personality, in psychiatric profiles and in the experience of chronic work and social hassles (TICS) were not statistically significant. *Cortisol awakening response* - The repeated measures ANOVA revealed comparable cortisol release profiles between the TTC and NSTEMI patients p=0.918, r=0.05, 95% CI effect −0.29 to 0.38. -Takotsubo cardiomyopathy (TTC) patients felt significantly more nervous than controls at arrival, post stress and at the end of examination (*p<0.05, **p<0.01.	-Is the exposure to the stimuli measured and evaluated equally between case-control? YES, there are no exact stimuli, but all the groups underwent the same stress measurement and psychiatric examination. -Is the one who measured the exposure blinded for the different groups (case-control)? No, not mentioned in the article.
Despite the small sample size, a trend for a blunted cortisol stress response and high incidences of stressful life events can be observed in TTC patients.	Cortisol awakening response: Saliva was collected immediately after awakening, as well as 15, 30, 45 and 60 min thereafter. On a quiet day and not to eat, drink or brush their teeth during the sampling period. Further record their sleep duration, store their samples cool and return them promptly. Psychological assessment: previous histories and current statuses of psychiatric disorders explored by the medical records and direct interviews. Self-report questionnaires were used to assess psychiatric and somatic symptoms, personality traits, and chronic distress within the 2 years before cardiac event and current mood. Stressful life events were investigated using a shortened version of Tennant and Andrews's life-event inventory.	*Stress response* - TTC patients tended to a significantly lower overall cortisol release (AUCg) than the controls (MDdiff=−10.3 nmol/L, 95% CI −21.3 to −0.8, r=0.35, 95% CIeffect 0.04 to 0.60; - No statistically relevant difference in the overall cortisol release was found in comparison with the NSTEMI patients - In response to the stressor the TTC patients showed significantly lower cortisol levels than the controls 15 min 95% CI and 45 min post stress 95% CI. - No statistically relevant differences were found in comparison with the NSTEMI patients in response to the stressor after 15 and 45 min.	*Strengths:* - Screened in detail for predisposing attributes - This was the first study done to identify psychological and hormonal parameters in TTC patients contrasted with patients who have made an equivalent experience of a heart attack. - They mention literature which substantiate their findings.
Institution, Country	*Statistical analysis:* Shapiro-Wilk tests Student t tests, or non-parametric Mann–Whitney tests, were used to analyse group differences for pairwise comparison. For categorical variables, Pearson's χ2 or Fisher's exact test were used. To perform analysis for ANOVA Greenhouse–Geisser correction was performed.	*Heart rate* -For each group, a significant increase in heart rates (bpm) from prestress to post stress could be observed which confirmed the efficiency of the stress experiment. No relevant group differences could be found in pairwise comparisons. -TTC patients felt greater nervousness than the control.	*Limitations:* -Small sample size - Missing timeline - No exclusion criteria - Lack of information about comorbidity in the case and control group. -Is NSTEMI better comparator than STEMI? and why they made the choice
Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany	ANCOVA: by inserting the poststress cortisol level as the dependent variable, (AUCg) using the formula from Pruessner et al. Paired-sample Wilcoxon test To compare the ratio between subjective and objective stress, MDMQ and cortisol data were z-transformed and adjusted; All p values reported are two-sided. The statistical significance was set at p<0.05. p Values of multiple testing were controlled using the false discovery rate from Benjamini and Hochberg. For the primary endpoints, effect sizes were calculated using Pearson's correlation coefficient r.	- The mean ratio between subjective and objective stress response (▲ 'nervousness'/ ▲ cortisol) in TTC patients was 1.9±6.1 SD, with no significant difference when contrasted with the NSTEMI patients (−1.8±13.4 SD) but with a trend towards a significant larger ratio when contrasted with the controls (−2.3±8.4 SD; mean difference=4.19, 95% CI−0.64 to 9.02, p=0.087).	- Recall/ reporting bias - Sampling of saliva at home, without defined criteria (e.g timeline). -Only one psychologist involved. - Uncertain whether the inclusion of females exclusively was random or intentional.
Year of data sampling			
Not defined. They refer to another link in the article, for additional information, which the university did not had access to.			

Reference: Yerasi C, Koifman E, Weissman G, Wang Z, Torguson R, Gai J, et al. Impact of triggering event in outcomes of stress-induced (Takotsubo) cardiomyopathy. Europ Heart J Acute Cardiovasc Care. 2017;6(3):280-286.	Design: Case series	
	Documentation	3
	GRADE	Moderate

Purpose	Materials and Methods	Results	Discussion and Comments
Aim of the study was to describe experience with stress – induced (Takotsubo) cardiomyopathy and in particular to examine the effects of the underlying trigger on outcomes	*Sampling:* retrospective review of medical records of 345 consecutive patients treated at Medstar Washington Hospital Centre from 2006 – 2014. *Data collection:* The Medstar Cardiovascular Research Network maintains a registry of patients clinically diagnosed with "stress cardiomyopathy" or TS (Takotsubo syndrome). The clinical records of all patients with these diagnoses were reviewed, and 345 met the inclusion criteria.	*Patient characteristics:* -The mean +- SD age of all the groups was 72 +- 12 (13) and 91% were women - There was a higher prevalence of African – Americans (32%) in the "medical illness" group -80% had hypertension -25% had diabetes mellitus -57% had hyperlipidaemia -20% had a psychiatric history -15% had endocrine disorders -22% had pulmonary disorders -13% had oncologic disorders -28% were smokers	Was the study based on a random selection from a suitable patient group? YES Was it ensured that the selection is not too selected? YES Were the inclusion criteria for the selection well defined? Unclear, TS is not defined by Mayo criteria Were all the selected patients in the same stage of a specific disease? NO, patients were grouped by different triggering events (mentioned in materials and methods)
Conclusion	Inclusion criteria were acute cardiac symptoms at presentation, a characteristic left ventricular contraction pattern (typical, atypical), and no major obstructive coronary artery disease. Patients were grouped based on their triggering event:		
Different triggers for Takotsubo syndrome confer different prognoses, with medical illness conferring the worst prognosis. The in – hospital death rate was low and mostly related to non – cardiac death secondary to the underlying medical illness	A: Medical illness: 126 B: Post – operative period: 24 C: Emotional distress: 33 D: No identified trigger: 162 Baseline demographic characteristics, death in hospital, length of stay in hospital, and cardiac complications were abstracted from the patients` medical records	*"Apart from these demographic factors, the observed "statistically significant" differences can be disregarded because most, if not all, can be accounted for by the differences in the underlying illnesses that formed the basis of their assignment group"* *ECG and laboratory findings:* -QT – intervals were prolonged in all four patients' groups. The PR interval and QRS duration were also similar between groups - ST – elevation, T wave inversions, troponin levels and creatine kinase MB differed between groups	Was the follow up sufficient (type/content /time) to highlight endpoints? YES Were objective criteria used to measure endpoints? YES When the case series are compared, are the series well described and are the distribution of prognostic factors described? YES Was the registration of data prospective? YES, the registration was prospective, but the study was a retrospective review
Institution, Country	*Statistical analysis:* A dedicated data coordination centre carried out all the data management and analyses using SAS 9.2. Continuous variables were expressed as mean +- SD or median (25 – 75th interquartile range) values according to the variable distribution. Students t – test was used to compare continuous variables and the chi – square test or Fisher`s exact test to compare categorical variables. To assess paired data, the paired Student`s t – test or Wilcoxon signed rank test was used as appropriate. The significance level was set at p < 0.05	*Coronary angiography:* -Arteriographic findings had the same frequency in all groups - "Luminal irregularity" was found in 75%, but no patient had an obstructive stenosis (> 50%) in a major coronary artery	
Washington DC, USA. Medstar Washington Hospital Centre		*Left ventricular function:* -90% of patients had typical TS, while atypical (basal/global/mid - ventricle) was noted in 10% -The degrees of left ventricle dysfunction were similar across the four groups	*Strengths:* -The researchers refer to other studies which strengthens their results -Materials and methods were done thoroughly -Adequate sample size -The authors are critical to the significance of observed results
Year of data sampling		*In – hospital death rate:* the overall death rate was 12 (3.5%), and 10 of the deaths were not cardiac – related. Patients with severe medical illness had a significantly greater death – rate (7.1%). These patients also had more severe nonfatal complications. Medical illness (Odds ratio (OR) = 6.25, confidence interval (CI) = 1.3 – 3.3, p = 0.02) and ST segment elevation (OR = 5.71, CI = 1.01 – 32, p = 0.04) were significantly associated with death	*Limitations:* -Researchers have not defined TS based on Mayo criteria for Takotsubo Cardiomyopathy. Because of this we do not know if all of the 345 patients actually had TS. This is especially problematic because one of the Mayo criteria for Takotsubo is absence of pheochromocytoma, while 15% of the patients in this study had endocrine disorders, and 13% had oncologic disorders (which could include pheochromocytoma) -A high percentage (47%) of patients with an unidentified trigger -2 patients missing in figure 1: "In – hospital mortality for patients with Takotsubo syndrome"
2006 - 2014			

Reference:	Design: Case – control / Cross sectional	
Compare A, Bigi R, Orrego PS, Proietti R, Grossi E, Steptoe A. Type D personality is associated with the development of stress cardiomyopathy following emotional triggers. Annals of Behavioral Medicine. Jun 2013; 45(3):299-307.	Documentation	3
	GRADE	Moderate

Purpose	Materials and Methods	Results	Discussion and Comments
This study sought to examine whether type D personality can be identified in SCM (stress cardiomyopathy) patients	*Sampling:* 3-year period (years not specified) *Cases (stress cardiomyopathy with emotional triggers and stress cardiomyopathy without emotional triggers)* were admitted consecutively to the researcher's hospital – based specialized cardiovascular clinics. Careful history taking identified whether significant stressful event immediately preceded the presentation of stress cardiomyopathy. Preliminary assessment of trigger events was carried out by cardiologists during admission to the emergency unit.	*Clinic and lab* Patients with AMI had significantly higher levels of troponin T, creatine kinase MB fraction, white cell count, hypertension, and systolic blood pressure compared with SCM patients *Emotional trigger events* -Loss experiences through death or separation from someone close were the most prevalent emotional	Were the case-control groups recruited from comparable populations? YES Are the groups comparable in regard to important background factors? YES Is the case group's condition sufficiently described/validated by
Conclusion	*Controls (myocardial infarction (AMI) with reported emotional*	triggers in both the SCM and AMI groups	diagnoses? Unclear: Mayo criteria for SCM are not sufficiently
-The results highlight the possible link between type D personality and increased biological reactivity to acute emotional stress -The key role of social inhibition of negative emotions as a characteristic of type D personality in emotionally triggered stress cardiomyopathy patients, emphasizes the importance of emotional regulation process in biological reactions to acute emotional stress. This implies that the risk of a stress cardiomyopathy event may depend not only on the individual`s cardiovascular vulnerability following stress exposure, but also on his or her coping mechanisms.	*triggering):* Over the same period of stress cardiomyopathy enrolment, the first consecutive 37 AMI patients who reported acute emotional triggers, and who 1:1 matched case on socio – demographic variables, were selected from a larger population of more than 300 acute myocardial infarction admitted to the emergency unit. SCM with emotional triggers: 37 SCM without emotional triggers: 37 AMI with emotional trigger: 37 *Data collection:* Two clinical psychologists who were blind to the patients` group interviewed all patients within 8h of initial screening in order to avoid memory distortion effects. Interviews involved a thorough assessment of emotional trigger events that occurred within 48h of symptom onset. Assessment of emotional trigger events was carried out using the Interview for Recent Life Events which specifies 64 different life events in nine areas. The reliability coefficient between the two interviewers was 0,88. Type D personality assessment was performed by two different clinical psychologists 3 months after initial screening by using the Type D scale (DS14) and without knowledge of the clinical diagnosis of the patients.	-The overall severity score for emotional triggers and their timing did not differ significantly between the two groups *Type D personality* -Analysis of type D as a categorical construct showed that of the 37 SCM patients with emotional triggers, 28 (76%) were categorized as type D compared with 13 (43%) SCM patients without emotional triggers and 12 (32%) AMI. The difference was significant between SCM with emotional triggers and SCM without emotional triggers and AMI, and between SCM without emotional triggers and AMI -SI (Social inhibition) scores were higher in patients with emotionally triggered SCM than non – emotionally triggered SCM or AMI (p < 0.01). The differences were significant between SCM with	described Does the control group have the current disease? NO Have the authors considered important confounding factors in the analysis? Unclear: the authors have only categorized SCM with emotional triggers where the trigger has been present during the last 48h before symptom onset, while other studies show that SCM can be due to continuous stressful events
Institution, Country	*Statistical analysis:* To detect a medium effect, assuming a 1:1 case – control ratio with an alpha level of 0,05 and power of 0,80 a conditional regression model and Monte Carlo simulation was used on a minimum of	emotional triggers and SCM without emotional triggers, and between SCM with emotional triggers and AMI, but not between SCM without emotional triggers and AMI	Is the exposure to the stimuli measured and evaluated equally between case-control? YES, there are no exact stimuli, but all the
Not specified	70 patients (35 cases and 35 AMI)	-NA (negative affectivity) differed significantly	groups underwent the same psychiatric examination and answered
Year of data sampling	Differences in categorical variables between groups were analyzed using	between SCM with emotional triggers and SCM	the same interview
Timeline: not specified	the chi – square test, while differences among groups were assessed by one – way ANOVA for continuous variables followed by Bonferroni – corrected post hoc test. Hierarchical logistic regression analyses with z – transformed negative affectivity and social inhibition scores, entering the main effect terms followed by the NA (Negative Affectivity = tendency to experience negative emotions such as dysphoria, anxiety, irritability, and negative view of self across time/situations) x SI (Social inhibitions = tendency to inhibit the expression of emotions/ behaviors in social interactions to avoid disapproval by others or feeling inhibited, tense, and insecure when with others) interaction, were used to test differences among groups. These analyses were adjusted for diabetes, history of CAD (coronary artery disease), systolic blood pressure, and hypertension since these factors may be particularly relevant. Final results are presented as adjusted odds ratios (ORs) with 0.95 confidence intervals (CI) and exact p values. Statistical analyses were performed with SPSS, version 18.0.	without emotional triggers in comparison with AMI but did not differ from each other. - After adjustment, the NA x SI interaction term distinguished SCM from AMI (OR = 1.72, 95% CI= 1.21 – 2.11, p= 0.03), indicating that the interaction between the two components is crucial -Within SCM, the odds of belonging to the SCM with emotional triggers compared with SCM without emotional triggers group were 1.11 (p = 0.04) for every unit increase in the NA by SI interaction and 1.86 (p = 0.02) in comparison with the AMI group. -Scores on the SI component also distinguished SCM with emotional triggers from AMI (OR = 1.92, p = 0.01) and SCM with emotional triggers from SCM without emotional triggers (OR = 1.53, p = 0.04)	Is the one who measured the exposure blinded for the different groups (case-control)? YES *Strengths* -This is the first study to examine whether type D personality can be identified in SCM patients -The two clinical psychologists who interviewed were blinded for participants and had a reliability coefficient in between them which were 0,88. *Limitations* -There are no other data in the literature on SCM with which to compare the results -Small sample size -The authors have not specified which 3 years they sampled data, nor if data was collected continuously or periodically. - The AMI comparison group was selected on the basis of reporting emotional triggers, so the prevalence of triggers is not representative of patients with AMI in general -The timing of the personality assessment. This was performed 3 months after hospitalization to allow the stabilization of the patients` emotional condition. Ratings could have been different if the assessment had taken place before the clinical episode -The authors have specified the study design as case-control and cross sectional, but not presented what they analyze as cross sectional nor discussed it through the article.

Reference:		Design: Case-Control Study (secondary analysis)	
Rosman L, Dunsiger S, Salmoirago-Blotcher E. Cumulative Impact of stressful life events on the development of Takotsubo Cardiomyopathy. Annals of Behavioural Medicine. Des 2017;51 (6):925-930.		Documentation	3
		GRADE	Moderate

Purpose	Materials and Methods	Results	Discussion and Comments
This study sought to examine associations between type, timing, and number of stressful life events and onset of TC	*Sampling:* March 2013- October 2015, New England. Only females enrolled. *Cases (TC)* were recruited among consecutive women presenting at emergency departments of three large medical centers in New England. *Controls* were women newly admitted with a diagnosis of acute myocardial infarction (MI) at the same centers and a group of healthy female controls (HC) recruited from a registry of research volunteers at the University of Massachusetts Medical School	-Demographic characteristics were similar across groups with the exception of income and education, which were higher in the HC group	Were the case-control groups recruited from comparable study populations? YES
	TC: 45 (case)	-History of anxiety disorders were also more prevalent among TC cases than MI and HC controls.	Is the case group's condition sufficiently described/validated by diagnoses? YES
Conclusion	MI: 32 (control)	-In regard to the type of event, TC women were significantly more likely to report the recent death of a spouse, close friend, or relative compared to MI or HC during the previous	
-Their results show that type of stressful event and exposure to repeated stressful events, rather than temporal proximity to the event, may play a role in the onset of TC. - The occurrence of TC was associated with certain life events (death, medical illness, or injury to a close friend or relative) But not with others.	HC: 30 (control) *Eligibility criteria for cases*: Female>21, be able to understand and speak English, have access to a telephone, have a first diagnosis of TC fulfilling Mayo Clinic diagnostic criteria. *Ineligible for cases:* unable or unwilling to give informed consent, had a history of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy; had dementia or cognitive impairment (from medical record),were clinically unstable. *Eligibility for controls (MI):* The control groups were women admitted with a confirmed diagnosis of acute (both ST elevation and non-ST elevation) myocardial infarction (MI). *Exclusion criteria* here were a prior diagnosis of TC, rest were same as cases *Eligibility for controls (HC):* were no previous diagnosis of stress cardiomyopathy or chronic conditions (any cancer other than non-melanoma skin cancer; cardiovascular disease; liver failure; renal failure), additional criteria were same as for cases.	6 months (p = 0.006). -Recent illness or injury to a close friend or relative was also significantly more prevalent in TC cases compared to both MI and HC (p = 0.001), while the prevalence of injury or illness to self, did not differ between TC and MI. -The mean total number of stressful life events significantly differed between groups (p < 0.001) with TC women reporting a greater number of prior stressful life events than MI or HC women -TC women were more likely to endorse experiencing multiple (3 or more) stressful life events compared to MI or HC controls, whereas MI controls were more likely to report a single stressful event prior to their cardiovascular event, and HC women were more likely to report none -TC cases were not significantly more likely than MI to experience a stressful life event within 1 month prior to their index hospitalization (p = 0.96).	Does the control group have the current disease? NO Have the authors considered important confounding factors in the analysis? YES Is the exposure to the stimuli measured and evaluated equally between case-control? YES Is the one who measured the exposure blinded for the different groups (case-control)? YES *Strengths:* -First study that direct attention towards cumulative stress and TC. May provide critical insight into the pathogenesis of TC -Confounding factors discussed. - Population included is appropriate to the study purpose. - Opportunities for early intervention and prevention may be provided by clinician attention to the symptoms of chronic stress in risk groups.
Institution, Country	*Data collection*: Interviewers and study participants were blinded to the study outcomes and to participants' case or control status. Stressful life event		*Limitations:*
Medical centers in New England, USA	information was systematically collected one month after hospital discharge using PERI Life Events Scale, during a telephone interview, focusing on the last 6 months before hospitalization.		-Small study population challenges the ability to evaluate the results significance. - Although women are most effected by TC, the actual population in
Year of data sampling	*Statistical analysis*: ANOVA was used to evaluate group differences, Chi-square for categorical outcomes and to compare mean total number of stressful life events Kruskal- Wallis test was used. For all estimates, p values or 95% confidence intervals were calculated. All analyses were performed with SPSS version 22.0		this study cannot be applicable to the majority of TC cases, due to sample size. - Recall bias -Subjective responses are not measured which may affect the outcome. - Minimal ethnical variation. -This was the first study done to examine associations between type, timing, and number of stressful life events and onset of TC.
March 2013-october 2015			

Reference:		Design: Case-control study and Interview done prospectively
Delmas C, Lairez O, Mulin E, Anxiodepressive Disorders and Chronic Psychological Stress Are Associated With Tako-Tsubo Cardiomyopathy. Circulation journal 2013;77(1):175-80. Epub 2012 Sep 13.		**Documentation** 3
		GRADE Low/Moderate

Purpose	Materials and methods	Results	Discussion and Comments
Characterize the prevalence of anxiodepressive disorders (ADD) and the chronic psychological stress (CPS) in patients with TTC or acute coronary syndrome (ACS). Done by using systematic screening with psychiatric interview.	*Sampling:* January 2010-December 2011, France *Cases:* 45 (Total 51, where 6 were excluded) consecutive patients with TTC admitted, were prospectively included. *Takotsubo inclusion criteria:* (1) acute cardiac event such as chest pain, dyspnea or syncope; (2) new electrocardiogram (ECG) abnormalities (ST elevation, T-wave inversion or abnormal Q-waves); (3) left ventricular systolic dysfunction with wall motion abnormalities extending beyond a single coronary perfusion bed (especially transient akinesia or hypokinesia of apical and midventricular segments with basal hyperkinesia); (4) absence of significant obstructive coronary artery disease (i.e., $\leq$50% luminal narrowing) or angiographic evidence of acute plaque rupture in the 3 major epicardial coronary arteries; (5) absence of myocarditis or typical ischemic late gadolinium enhancement on cardiac magnetic resonance imaging (CMRI); and (6) absence of pheochromocytoma *Controls;* 50 patients admitted for ACS with troponin elevation and matched for age and sex were prospectively included. ACS with troponin elevation including (STEMI) and (NSTEMI) were diagnosed according to the European Society of Cardiology guidelines. *Data collection: (interview and MINI done prospectively):* All patients were questioned about their medical history and underwent a standard evaluation with clinical examination and 12-lead ECG. Demographic data, cardiovascular risk factors, laboratory results and medications were taken from medical records. Obesity definition: BMI $\geq$30 kg/m^2. Troponin C was measured on admission and at several times during the in-hospital stay, and only maximum values were retained for analysis. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) formula. Left ventricular ejection fraction (LVEF) was assessed on transthoracic echocardiography (IE33, Philips Medical Systems) at admission and before discharge using the conventional apical 2- and 4-chamber views and the modified Simpson's method. Coronary and left ventricular angiography was performed. For TTC, coronary angiography was performed 24–72 h after admission and left ventricular angiograms were obtained at the same time in the right anterior oblique and left anterior oblique projections. For ACS, the timing of coronary angiography was chosen according to the European Society of Cardiology guidelines10 All patients with TTC underwent CMRI within 2 weeks after discharge, which confirmed complete recovery of LVEF and excluded myocarditis or myocardial infarction. Psychiatric assessment: patients were questioned about their lifestyle and psychotropic medications. CPS was defined by the presence of personal, familial or social difficulties reported by the patient, such as a dependent child or husband, recurrent familial or professional conflicts and recurrent recent deaths of close friends or relatives (at least 2 deaths in the last 2 years). The Mini International Neuropsychiatric Interview (MINI) was used for psychiatric assessment. Interview was performed within 48 h after admission. Current or past major depressive disorder, generalized anxiety disorder, dysthymia and post-traumatic stress disorder were selected for systematic psychiatric screening. Anxiodepressive disorders (ADD) were defined as the presence of current or past major depressive disorder and/or generalized anxiety disorder *Statistical analysis:* Baseline characteristics are summarized as mean ± SD for continuous variables. Association between categorical variables was investigated using the chi-squared or Fisher exact test when appropriate and the means of continuous variables were compared using a 2-tailed Student t-test. Differences were considered statistically significant for P<0.05. All analysis was performed using Statview.	-Among the 45 patients with TTC. 43 were female, of whom 41 were postmenopausal. There was no difference with the matched control patients. -At admission, patients with TTC suffered more often from dyspnea (49% vs. 24%, P=0.01) whereas chest pain was more frequent in those with ACS (67% vs. 96%, P<0.001). -More patients with ACS had ST elevation or ST depression at presentation than patients with TTC. -ECG changes at admission in patients with TTC were predominantly T wave inversion (44% vs. 10%, P<0.001) -As expected, patients with ACS had higher peak troponin than those with TTC (72.9±104.4 pg/ml vs. 6.2±9.4 pg/ml, P<0.001). They also had lower creatinine and better glomerular filtration rate than patients with TTC (74±25 ml/min vs. 89± 33 ml/min; P=0.004). -An acute stressful event within 72 h before presentation was identified in 35 patients (78%) with TTC vs. 9 (18%) with ACS (P<0.001). Triggering stress was emotional for 25 (56%) with TTC and 8 (16%; P<0.001) with ACS; and was physical for 18 patients (40%) and 3 (6%) with TTC and ACS, respectively (P=0.001) -In addition to an acute stressful event, CPS was found in 20 patients (44%) and in 9 (18%) with TTC and ACS, respectively (P=0.005). -There were 35 patients (78%) and 13 (26%) with ADD in the TTC and ACS groups, respectively (P<0.001). -Ten patients (22%) with TTC and 3 (6%) with ACS had both generalized anxiety disorder and major depressive disorder (P=0.03). *" The number of patients was too small for statistical analysis to be performed".* -CPS and/or ADD were found in 35 patients (78%) and in 18 (36%) with TTC and ACS, respectively (P<0.001).	- Were the case-control groups recruited from comparable study populations? YES -Is the case group's condition sufficiently described/validated by diagnoses? YES Are the groups comparable in regard to important background factors? YES -Does the control group have the current disease? NO. -Have the authors considered important confounding factors in the analysis? Unclear, some factors are highlighted, and others are not mentioned. -Is the exposure to the stimuli measured and evaluated equally between case-control? YES, there are no exact stimuli, but all the groups underwent the interview and psychiatric examination. -Is the one who measured the exposure blinded for the different groups (case-control)? NO *Strengths:* -Screened in detail for predisposing psychiatric factors. -Reflection around their findings -The researchers refer to other studies which strengthens their results - Material and methods were described in detail. *Limitations:* -Small sample size -Recall/reporting bias -Not mentioned if interviewer were blinded -There are many psychiatric measurement tools, not described why selectively MINI was used. Another point is only one tool for psychiatric measurement is used. -- The number of patients was too small for statistical analysis to be performed. - Timing of psychiatric interview, within 48 h after admission, may have affected the reliability and reproducibility of the diagnosis of psychiatric disorder. -A hypnotized study conclusion, with no statically analysis makes it less reliable. -Short timeline, only one hospital involved.
Conclusion			
ADD and CPS are common in patients with TTC and more frequent than in patients with ACS. This finding suggests that systematic effects of ADD and CPS could participate in the pathophysiology of TTC. This study shows for the first time, that in addition to an acute stressful event, ADD an CPS predispose to TTC.			
Institution, Country			
University hospital of Rangueil, Toulouse, France			
Year of data sampling			
January 2010-December 2011			